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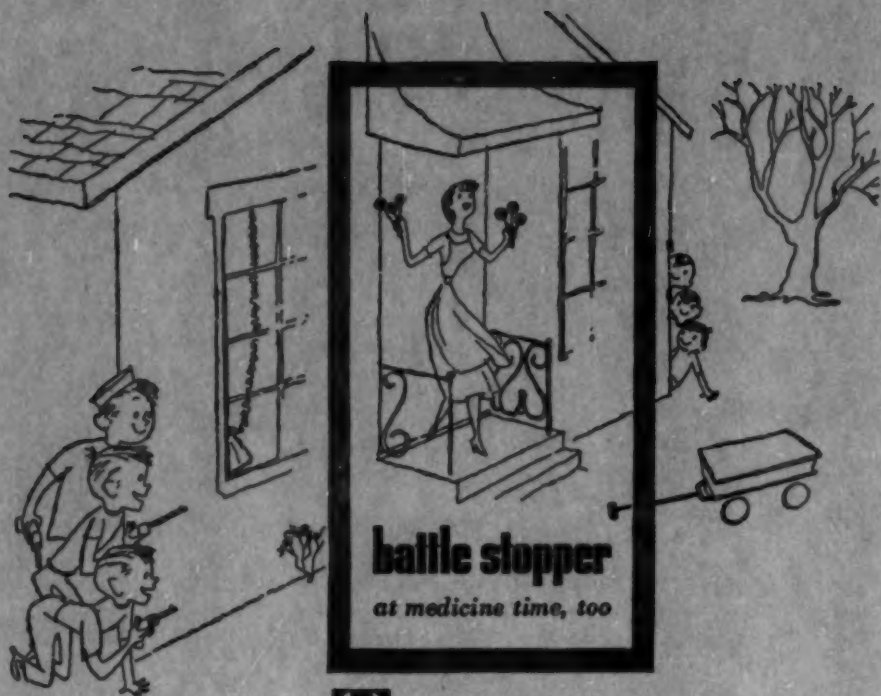
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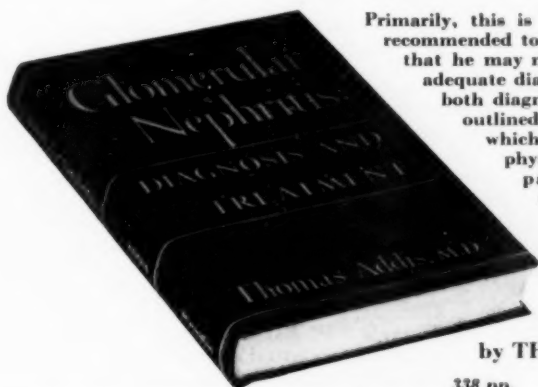
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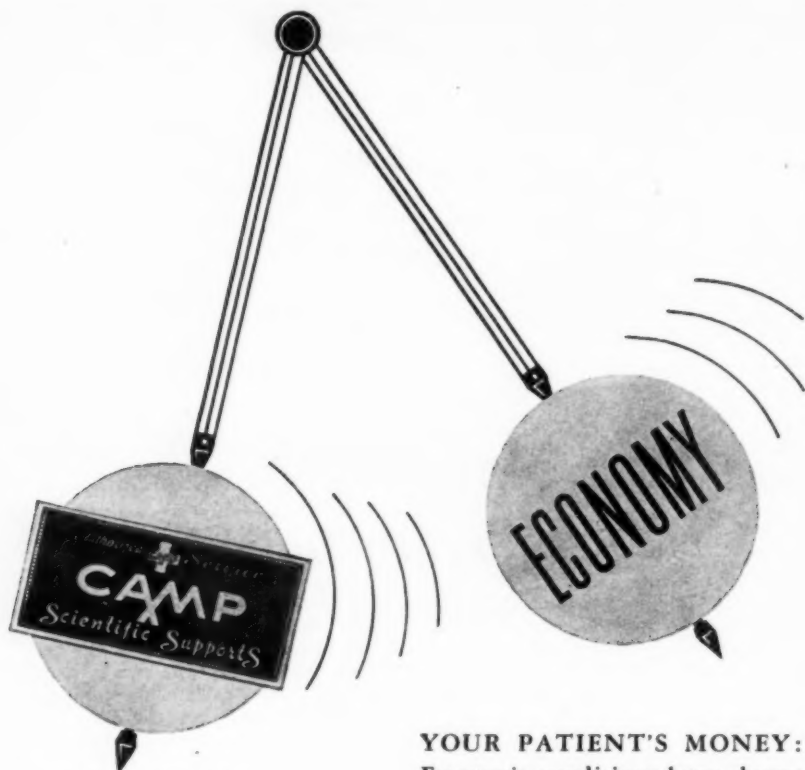
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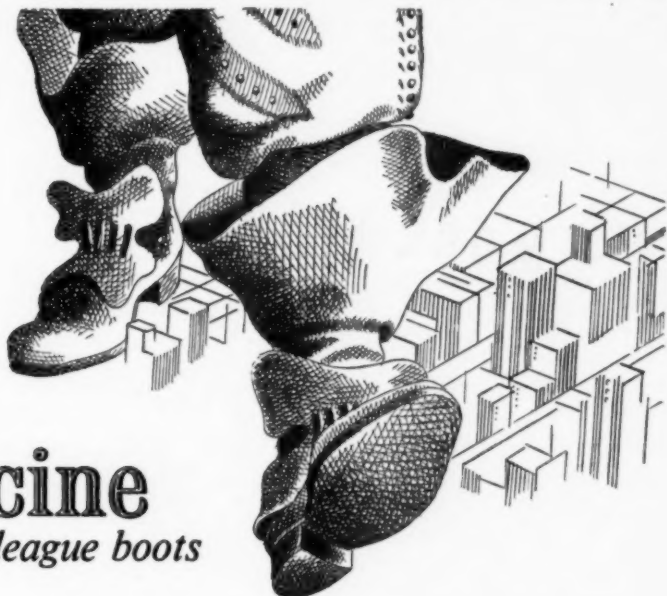
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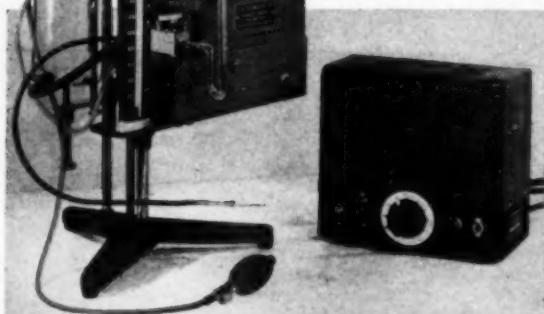
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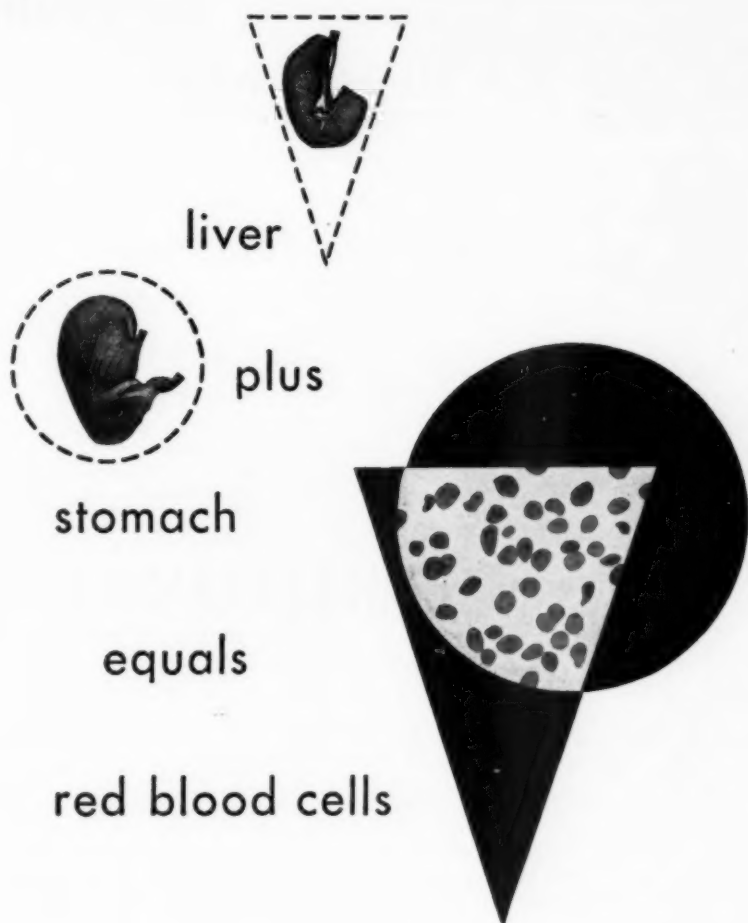
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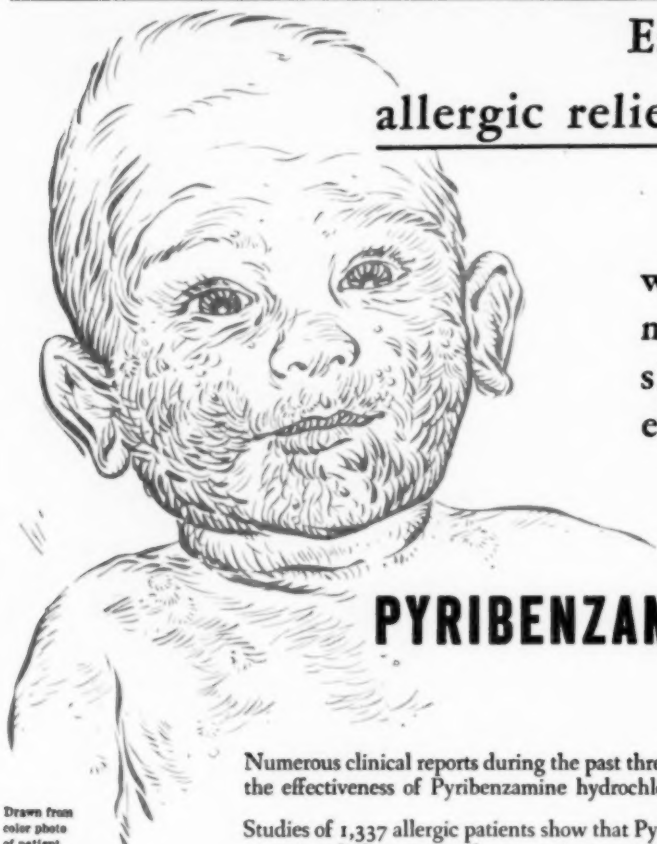
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1. Loveless, M. H.: *Am. J. of Med.*, 3: 3, 296-308, Sept. 1947.

2. Arbesman, C. E.: *N. Y. State J. of Med.*, 47: 16, 1775-81, Aug. 1947.

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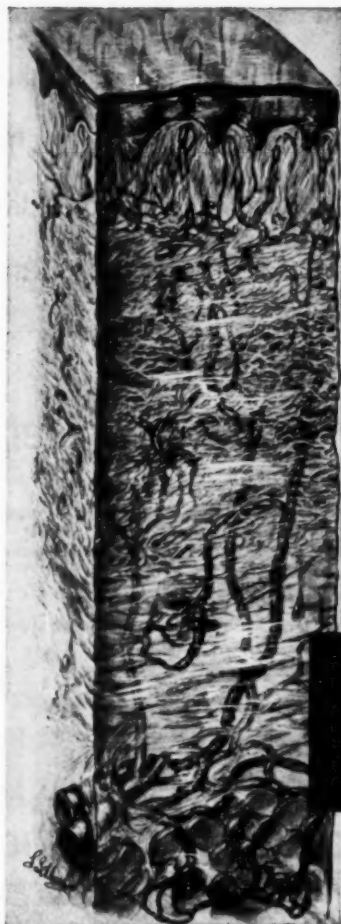
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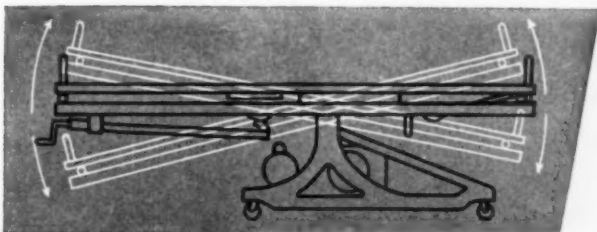
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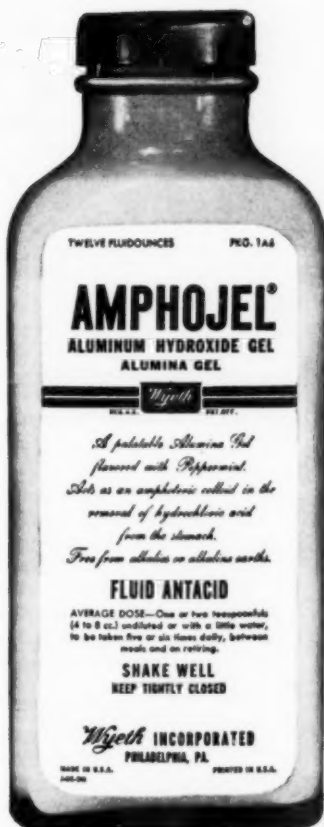
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(Am. J. Med., 5:100, 1948)

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ANNALS OF INTERNAL MEDICINE

VOLUME 30

APRIL, 1949

NUMBER 4

THE EFFECTS OF THE "RICE DIET" UPON THE BLOOD PRESSURE OF HYPERTENSIVE INDIVIDUALS*

By HENRY A. SCHROEDER, M.D., *St. Louis*, PALMER H. FUTCHER, M.D.,
Baltimore, Maryland, and MELVIN L. GOLDMAN,† M.D.,
St. Louis, Missouri

SINCE Kempner¹ reported alleviation of the elevated blood pressure in cases of arterial hypertension and renal diseases by the use of a diet composed of rice, fruit juices and vitamins, controversy has arisen regarding the manner in which this diet acts. One explanation for its hypotensive effect is that it is poor in salt, as it contains less than 0.5 gm. NaCl per day.² Other possible explanations are that the diet is lacking in unknown substances which may play a part in elevating the blood pressure, or less likely, that it contains some material capable of lowering an elevated blood pressure.

In order to evaluate the efficacy of this diet and to study more fully the mechanism by which it affects blood pressure, it was used in seven patients who were in hospital for relatively long periods of time. Modifications of the diet were subsequently made in several cases, in order to determine what substances, if any, when added would counteract its hypotensive effect. The experiences here reported throw light on the degree of change in blood pressure which one can expect in patients treated by this diet. In order to discover any special advantages of this diet, a comparison was made between these changes and those induced by restriction of salt and by hospitalization.

METHODS

Patients were selected at random from a group being studied in the Out-Patient Department of the Washington University Clinics, the only criteria

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From the Department of Internal Medicine and the Oscar Johnson Institute, Washington University School of Medicine and Barnes Hospital, St. Louis, Missouri.

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The assistance of Miss Dorothy Fraser, R. N., Miss Sallie Wood, R. N., Miss Marlene Hunter, Dietitian, and Miss Julia E. Finn is gratefully acknowledged.

† National Institute of Health Postdoctorate Research Fellow.

being that they suffered from arterial hypertension, that the non-protein nitrogen content of their blood was normal, and that they were willing to remain in hospital for a minimum period of three months. The diet, as prescribed by Kempner (hereinafter called the "rice diet") consisted of three daily feedings, each supplying:

Rice—90 gm. dry weight,
Sugar—as desired; 25 gm. average,
Fruit juice—200 c.c.,
Fruit—2 servings.

The sodium content did not exceed 0.2 gm. Approximately 1750 calories and 24 gm. of protein were supplied daily. Ferrous sulfate, 0.6 gm. and three multivitamin tablets (Upjohn, Unicaps) were administered daily, except in the case of one (A.P.) who was given *Multivits* (White).

Patients spent the whole period of observation in Barnes Hospital, four being allowed out of bed as desired, and three restricted to bed. Blood pressure was measured once or twice a day with the patient in the supine position; the determination in the morning was made before the patient arose and before breakfast, and that in the afternoon after one hour of rest. An

TABLE I
Effect of Diet Upon Blood Pressure and Body Weight

No.	Patient	Age Years	Control Period			Experimental Period			Change in Blood Pressure mm. Hg		Weight (lbs.)		Total Hos- pital Days
			NaCl in Diet Gm.	Dura- tion Days	B. P.* mm. Hg	Diet or NaCl Content Gm.	Dura- tion Days	B. P.* mm. Hg	Sys- tolic	Dias- tolic	Initial	Change	
1	L. S. ♀	42	21	21	191/108	Rice	31**	169/88	-22	-20	182	-10	92
2	S. K. ♀	56	2	13	232/119	Rice	16	224/119	-8	0	104½	-1½	34#
3	A. K. ♂	43	5-8	26	204/119	Rice	21	197/113	-7	-6	154	-1	90
4	L. M. ♂	36	5-8	51	198/134	Rice	25	177/128	-21	-6	129½	-10½	102
5	C. O. ♀	38	5-8	34	156/107	Rice	21	126/93	-30	-14	125	-10	120
6	A. F. ♂	39	5-8	32	168/112	Rice	35	137/93	-31	-19	129	-8	103
7	A. P. ♂	42	1	31	251/163	Rice	90	226/162	-25	-1	117	-13½	121
8	L. C. ♀***	33	8	23	199/123	1	21	167/106	-32	-17	233½	-13	—
9	W. D. ♂	43	5-8	28	190/119	1	24	164/109	-26	-10	226½	-12	98
10	F. W. ♀†	23	8	40	183/115	1	50	162/118	-21	+3	144	-7	114
11	I. H. ♀†	40	2	35	148/101	12	23	161/110	+13	+9	187½	+6½	90
8	L. C. ♀***	33	1	21	167/106	8	10	190/119	+23	+13	220½	+6	—
12	D. B. ♀	25	5-8	10	172/111††	5-8	85	143/100††	-29	-11	115	+3½	95
10	F. W. ♀†	23	5-8	14	193/131††	8	40	183/115††	-10	-16	151	-7	—
11	I. H. ♀†	40	2	10	165/115††	2	35	148/101††	-17	-14	192½	-5	—
13	V. R. §	42	8	10	193/126††	8	39	168/113††	-25	-13	130	+5	92

* Average of all blood pressure readings made during last 7 days of period.

** Pt. received 6 gm. additional NaCl daily for 15 days from 32nd to 46th day. Total duration rice diet 65 days (see figure 1).

Died.

†† Average of first 10 and last 10 days of period of observation.

*** 1000 calorie diet throughout hospital stay.

† 1200 calorie diet.

§ Case not reported in detail. Renal function was normal and ocular fundi showed only arteriolar narrowing.

observation period of 13 days to seven weeks in hospital served as control during which a normal diet (restricted as to salt or caloric content in three cases) was given. The intake of fluids was not limited. The rice diet was then given for 16 to 90 days (table 1), and a normal diet finally substituted. In two cases an attempt was made to evaluate the effect of adding sodium chloride to the rice diet. All patients except A. K. received a barbiturate sedative each evening throughout the greater part of their hospital stay. The effect upon the blood pressure of three doses of 0.18 gm. of sodium amytal administered at hourly intervals ("sodium amytal test") was measured in four patients during the control period.

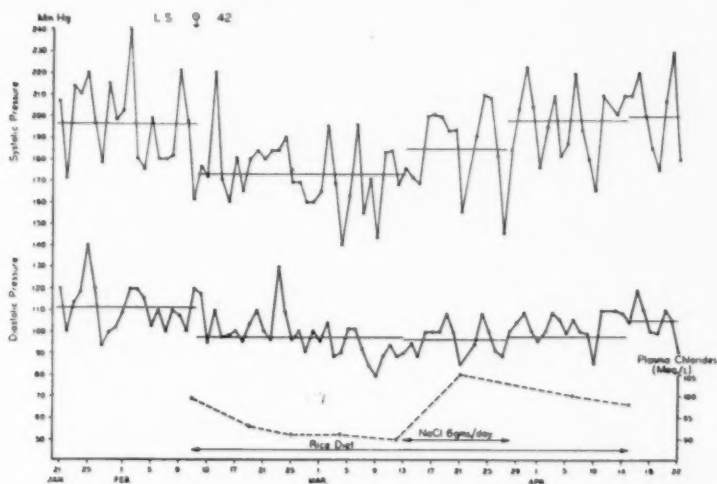


FIG. 1. Case 1, L. S. The straight lines indicate average of all blood pressure measurements recorded during the indicated period of observation. The control period lasted 21 days with the patient on bed rest. From February 11 through March 8 she was allowed up one hour twice daily, thereafter she was up as desired. "Rice Diet" indicates the unmodified diet as described in the text. Before the "Rice Diet," patient was taking a diet containing 2 gm. sodium chloride and 1200 calories. After it, she was given a high protein diet restricted to 1000 calories. Six gm. of salt per day were added to the rice diet from March 13 to 28.

RESULTS

Method of Analysis: The average systolic and diastolic pressure, shown in figures 1 to 9, was calculated from all recorded blood pressures measured during the whole of each period. In order to demonstrate greater changes, if present, however, the average blood pressures for the last seven to 10 days of each period were calculated and shown in table 1. This shorter period, while reflecting changes occurring slowly, may be less accurate an indication of the actual state of affairs.

Effect of Rice Diet on Blood Pressure after Control Period: Four of seven patients, A. K., L. M., A. P. and S. K., exhibited a fall in average diastolic blood pressure of less than 6 mm. Hg calculated from readings made during the last week of each period. Of these, S. K. took a normal diet restricted to 2 gm. of salt during the control period, and A. P. one restricted to 1 gm. (table 1). The blood pressures of these four patients were in a relatively

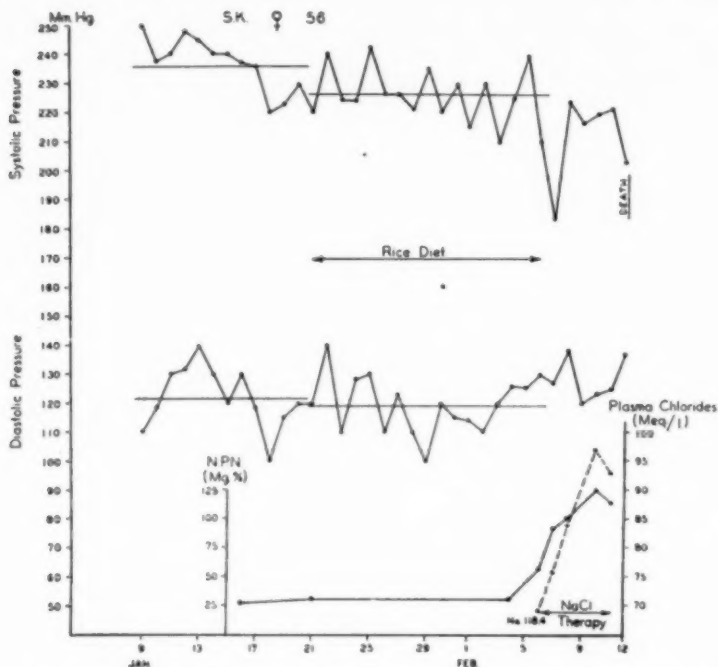


FIG. 2. Case 2, S. K. N.P.N. indicates non-protein nitrogen in the blood. Other notations same as figure 1. Patient remained in bed during study. Control period lasted 13 days. Before the "Rice Diet," the patient was given a normal diet containing only 2 gm. sodium chloride. At NaCl therapy, 33 gm. of sodium chloride were given intravenously in hypertonic solution. Note the absence of significant change in diastolic pressure in spite of a plasma sodium level of 118.4 mEq/l. (See case report.)

high range during the control period, and the change produced by the rice diet was insignificant (figures 2, 3, and 6)* since the maximum diastolic fall was 6 mm. Hg. Fresh retinal hemorrhages appeared in A. K. after he had been on the rice diet for several days.

Of the remaining three patients, two, A. F., and C. O., subsisted on a normal diet unrestricted as to salt during the control period, and one, L. S.,

* As insignificant changes in blood pressure occurred in A. K., his chart is omitted.

was given 1200 calories restricted to 2 gm. of salt. Their blood pressures were less elevated during the control period than the others and fell to a level slightly above normal during treatment with the rice diet (figures 1, 4, and 5).

Effect of Adding Sodium Chloride to the Rice Diet: For a period of 15 days, 6 gm. of salt were added to the rice diet ingested by two patients, L. S. and A. F. The blood pressure of A. F. was uninfluenced; that of L. S. rose slightly and continued to rise during a subsequent period of 18 days on the rice diet during which no extra salt was administered. In these two patients, therefore, the addition of salt to the rice diet produced no consistent effects during the period of observation (figures 1 and 5).

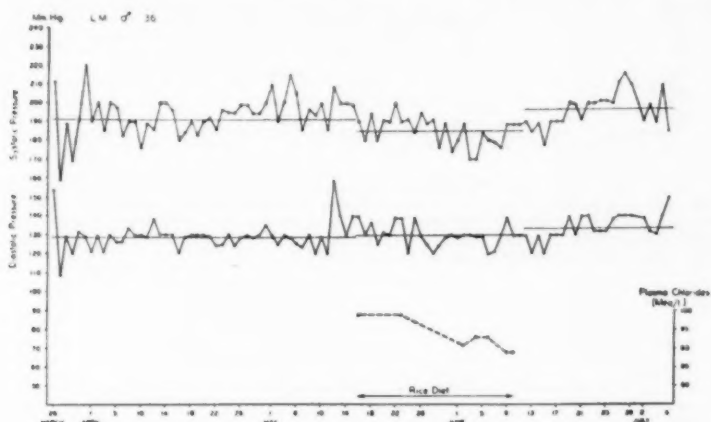


FIG. 3. Case 4, L. M. Patient was ambulatory. Before the "Rice Diet" patient was given a normal diet. After it, he was on a high protein diet. The control period lasted 51 days. Notations same as figure 1.

Effect of Adding Meat to the Rice Diet: The addition of 100 gm. of unsalted ground beef to the rice diet ingested by C. O. produced no changes in the diastolic blood pressure during an 11 day period of observation. The systolic blood pressure appeared to rise somewhat (figure 4).

Effect of Substituting a Normal Diet for the Rice Diet: Three patients were studied after a normal diet was substituted for the rice diet. After the rice diet was discontinued, C. O. was fed for 50 days a normal diet in which the intake of salt was restricted to 2 gm. In addition, she was given 6 gm. of sodium chloride daily. During this period the blood pressure rose moderately, reaching an average level approximately 20 mm. Hg systolic and 20 mm. diastolic higher than that observed on the rice diet (figure 4).

A. F., after a period of 16 days on the rice diet supplemented by salt, was placed on a high-protein diet unlimited as to salt content, with an additional

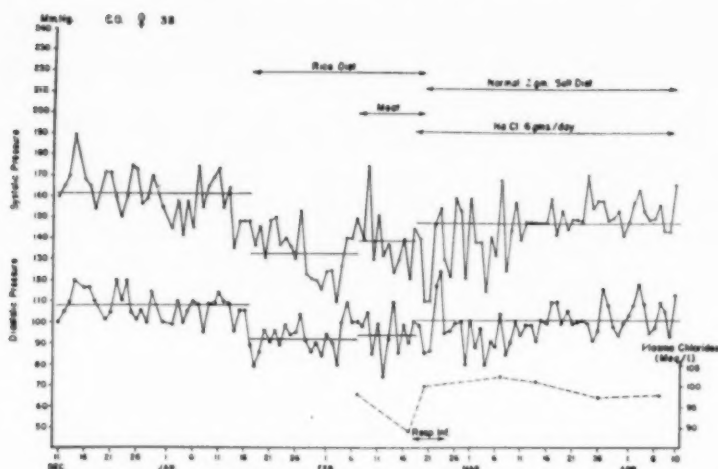


FIG. 4. Case 5, C. O. The control period lasted 34 days. Before the "Rice Diet" patient was on a normal diet. At "Meat" 100 gm. of unsalted ground beef steak was added to the rice diet. Subsequently, she was placed on a normal diet restricted to 2 gm. sodium chloride daily. Note that the level of her blood pressure was almost normal the day the rice diet was started. Notations same as figure 1.

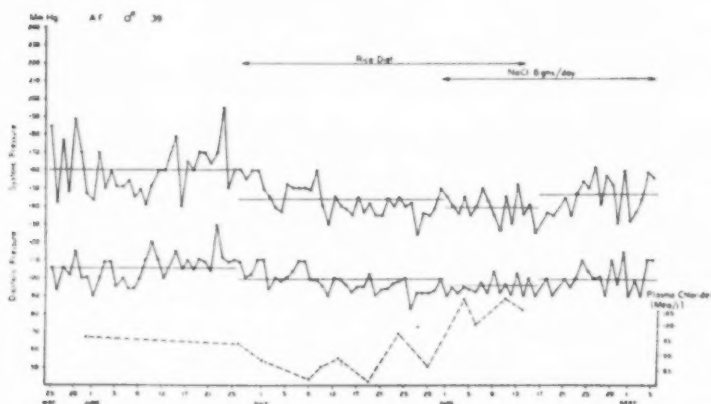


FIG. 5. Case 6, A. F. Patient was ambulatory. The control period lasted 32 days. On July 31, the serum volume, using the dye T-1824, was 2100 c.c.; hematocrit 39 per cent; blood volume 62.35 c.c. per kg. On August 9, serum volume was 2740 c.c.; hematocrit 39.4 per cent; blood volume 4521 c.c.; blood volume 82.6 c.c. per kg. Before the "Rice Diet," patient was on a normal diet. After it, he was given a high protein diet. From July 31 on 6 gm. salt daily were given in addition to the diet. Notations same as figure 1.

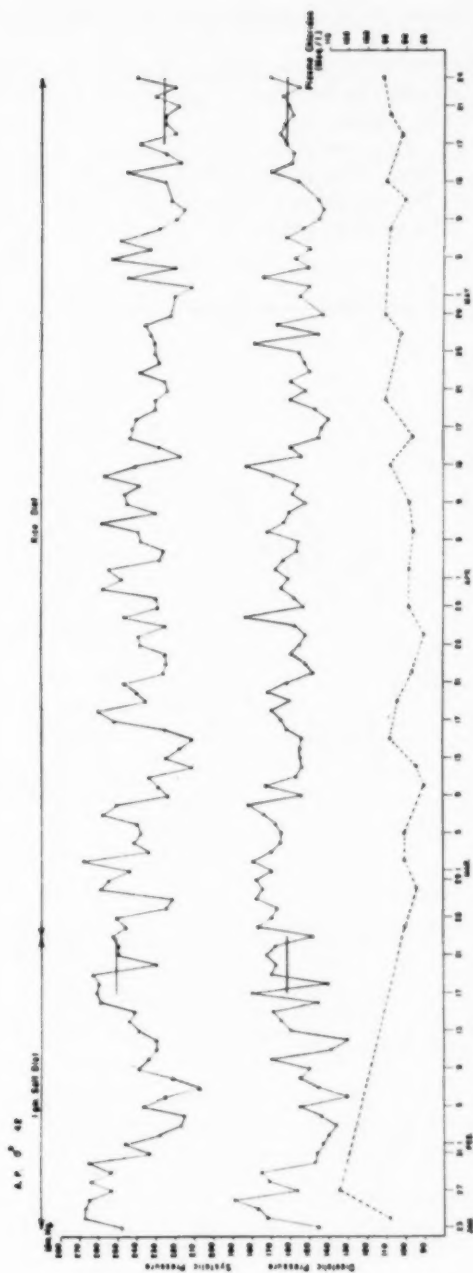


FIG. 6. Case 7, A. P. (Notations same as figure 1.) The control period lasted 31 days. During this period the non-protein nitrogen in his blood had risen from 26 mg. per cent on January 24, to 91 mg. per cent on January 28, and it had decreased slowly to normal levels by the time the rice diet was instituted. The clearance of urea was 33 per cent of normal before the rice diet was started, and 15 per cent of normal at the end without there being nitrogen retention.

6 gm. of sodium chloride daily. The average blood pressure, during 20 days on this regime, exceeded by less than 10 mm. Hg that of the last week of the unmodified rice diet (figure 5).

L. M., after the rice diet, was placed on a high protein diet unlimited as to salt content for 26 days. During this period his average blood pressure was higher by 19 mm. Hg systolic and 5 mm. diastolic than that observed during the last week of the rice diet (figure 3).

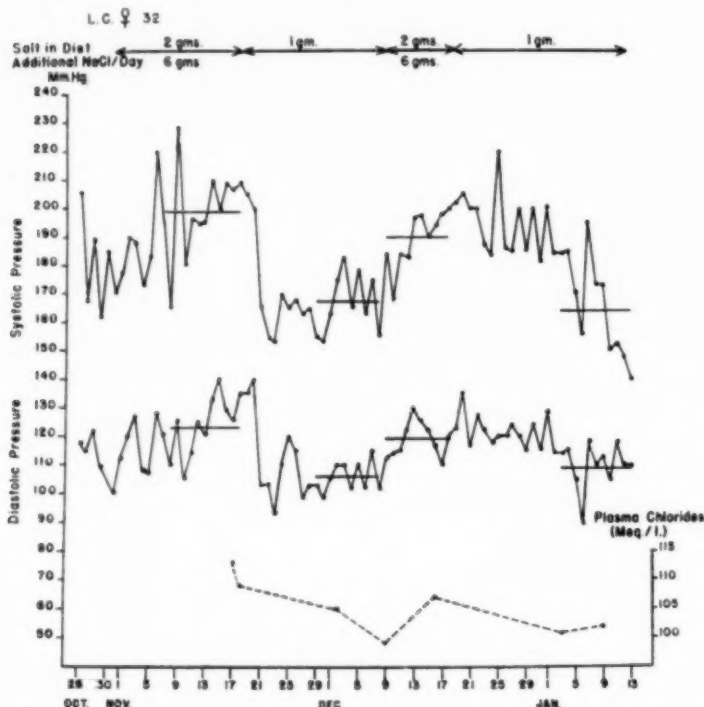


FIG. 7. Case 8, L. C. (Notations same as figure 1.) Throughout the period of observation, calories were restricted to 1000 per day. The control period lasted 23 days. For the first five days the patient was taking a diet unrestricted as to salt. She was ambulatory. Blood pressure levels were influenced by the intake of salt.

Therefore, in one of three patients the replacement of the strict rice diet by normal foods containing average, or higher than average, amounts of salt was associated with a moderate elevation of diastolic pressure above the levels observed while on the strict diet.

Observations on Plasma Chloride Concentrations: The administration of the rice diet was associated with a fall in plasma chloride concentration to a

range of 85 to 90 mEq. per liter in six cases and to 69 mEq. per liter in one (figures 1 to 6). There was no obvious correlation between changes in blood pressure and the plasma chloride concentration.

The rice diet did not significantly influence the serum sodium level in three patients with essentially normal renal function (table 2). Ingestion of this diet was associated with an unexplained increase in the normal discrepancy between the concentration of sodium and the sum of the concentrations of chloride and of carbon dioxide expressed as combining power.

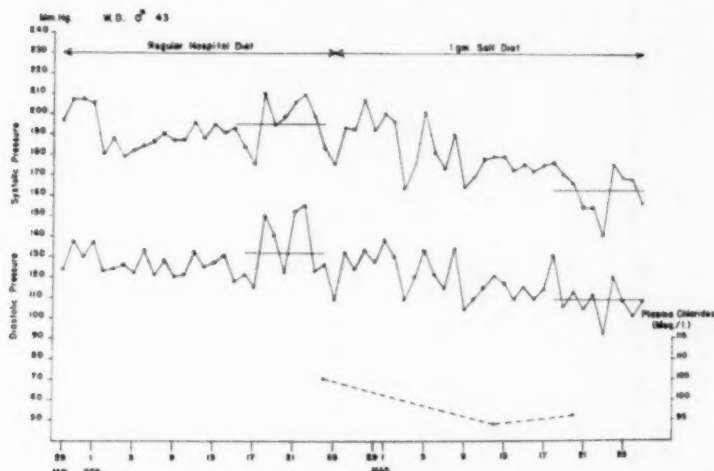


FIG. 8. Case 9, W. D. (Notations same as figure 1.) The control period lasted 28 days. Patient ambulatory. A normal diet was given before salt restriction was instituted. Note that blood pressure did not appear to be influenced until about three weeks after salt restriction was begun.

Effect of Rice Diet upon Patient with Impaired Renal Function: The renal function of S. K. was impaired at the start of the period of observation, but the non-protein nitrogen content of the blood was not elevated (figure 2). This patient's subsequent course is presented in detail in the protocol and the graphic chart. After she had ingested the rice diet for 16 days, the chloride content of her serum was found to be 69 mEq. per liter. Concomitantly, she developed oliguria and uremia, and she died a few days later. It seems likely that the rice diet precipitated the episode of uremia because of the restriction of salt which it imposed.

Miscellaneous Responses to Rice Diet: The patients found the diet very monotonous; some required considerable encouragement from the hospital staff before agreeing to complete the prescribed period of observation. Several complained of weakness, and five lost considerable weight. The diet did not influence significantly the normal concentrations of serum cal-

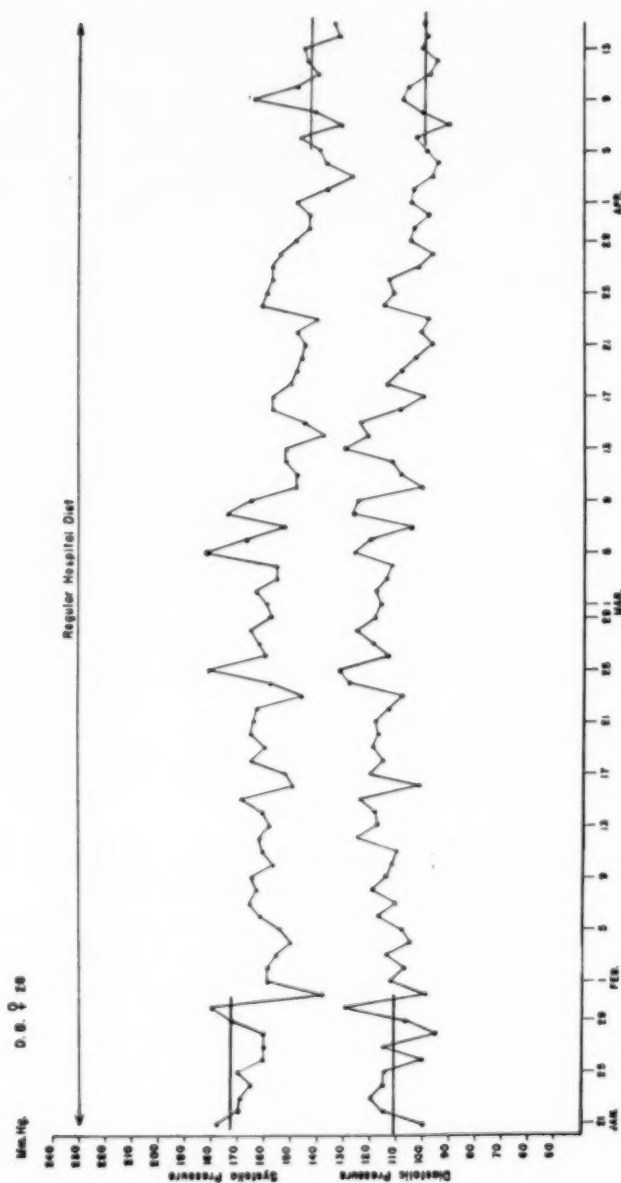


FIG. 9. Case 12, D. B. (Notations same as figure 1.) Patient was given a regular hospital diet throughout her stay. On April 1 a mild upper respiratory infection occurred lasting two days. There appeared to be a gradual decline in the level of blood pressure starting about March 15, that is after almost eight weeks in the hospital.

cium or serum phosphorus of three patients, A. K., L. M., and A. F., in whom measurements were made. The plasma proteins of one became lower; in a second, the values were divergent, but it is possible that they became lower. In four there were no significant changes (table 2).

The Effect of Moderate Salt Restriction on Levels of Blood Pressure: In an attempt to compare the results obtained on the rice diet with those expected from restriction of sodium chloride alone, three other patients were

TABLE II
Blood Proteins and Electrolytes as Influenced by the Rice Diet

Patient	Date	Total Gm. per 100 c.c.	Plasma Proteins Albumin Gm. per 100 c.c.	Globulin Gm. per 100 c.c.	Plasma Chloride mEq. per Liter	Plasma CO ₂ Combining Power mEq. per Liter	Serum Sodium mEq. per Liter
L. S.	Feb. 12*	7.2	4.1	3.1	100		
	Apr. 15†	5.5	3.3	2.2	98		
S. K.	Jan. 21*	6.4	3.8	2.6			
	Feb. 6†				69	24.1	118.4
	Feb. 7				76	25.5	
A. K.	Apr. 25*	6.9	4.9	2.0	98	27.0	
	Apr. 28				88	33.6	141.0
	May 16†	7.0	4.8	2.2	85	29.3	140.4
L. M.	May 16*	5.4	3.7	1.7	99	27.7	142.6
	June 10†	5.5	3.7	1.8	89	32.5	144.3
C. O.	Jan. 21*	6.3	4.3	2.0			
	Feb. 17				92	28.1	
	Feb. 18‡	6.3	4.3	2.0			
A. F.	May 31	5.7	3.5	2.2	96	31.1	
	June 26*	7.5	4.6	2.9	94	29.4	143.8
	July 29†	5.4	3.1	2.5	86	31.4	142.8
	Aug. 14‡	5.9	3.9	2.0	105	31.4	144.0
A. P.	Feb. 23*	—	—	—	90	30.5	—
	Mar. 28	7.1	4.7	2.4	89	35.0	—
	Apr. 30	7.4	4.6	2.8	95	—	—
	May 24†	7.7	4.9	2.8	96	30.6	—

* At institution of unmodified rice diet.

† At conclusion of unmodified rice diet.

‡ At conclusion of rice diet plus 100 gm. meat.

‡ At conclusion of rice diet plus 6 gm. sodium chloride.

studied under the same conditions (L. C., W. D. and F. W.). In one case, L. C. (figure 7), the average blood pressure fell significantly three days after restriction of salt from a daily intake of 8 gm. to one of 1 gm. This change was reversed after the salt intake was increased to 8 gm. and recurred again but at a slower rate, when the intake was reduced for the second time (table 1). In another, W. D. (figure 8), a significant fall in diastolic pressure occurred after prolonged salt restriction, and in a third, F. W., only the systolic level was affected. Weight was lost by all three, two being re-

stricted also as to calories. These changes were comparable to those seen on the rice diet. Four other patients (not included in table 1) were studied in a similar manner. The effect of salt restriction could not properly be evaluated because other influences may have entered the experiments. No effect of salt restriction was evident.

The Effect of Adding Salt to a Diet Previously Restricted: In one case, I. H., blood pressure had fallen slowly to near normal levels on a regular diet containing 2 gm. of salt. When 12 gm. additional salt in enteric coated capsules were given, her blood pressure rose moderately only to fall again when salt was restricted.

The Effect of Rest plus Salt Restriction: One patient, M. P., not reported in detail because she was inadequately studied, was put on a normal diet containing 1 gm. of salt on admission to the hospital. She was a 43 year old colored woman with relatively severe hypertension. Her average blood pressure for the first four days of her hospital stay was 220 mm. Hg systolic and 131 diastolic. During the last four days of her 15 day stay it had fallen to 140 and 95 mm. Hg, a change of 60 mm. Hg in the systolic level and 36 in the diastolic. The level of her blood pressure during one year's observation in the Out-Patient Department had been relatively "fixed" at the same or higher values as on admission, and she had suffered from severe headaches and symptoms referable to her heart. Such changes have been seen occasionally on the general medical service.

Effect of Hospitalization: One patient, J. O., also not reported in detail, was admitted for study of dietary influences on her blood pressure, which had for several months been approximately 175 mm. Hg systolic and 110 diastolic. She was a 43 year old, white woman who complained of nervousness, headaches, and cardiac pain. On admission her blood pressure was at the level stated, but after 20 days in bed on a normal diet, it averaged 120 mm. Hg systolic and 80 diastolic, a fall of 55 mm. and 30 mm. Hg. The dietary factor could, therefore, not be studied.

Three patients, D. B. (figure 9), F. W. and V. R., were studied in order to evaluate the effect of hospitalization on the levels of blood pressure (table 1). Diastolic pressures fell an average of 11, 16, and 13 mm. Hg after being in hospital 85, 40, and 39 days respectively. In one, the diet was restricted as to calories. These cases are mentioned only for the purpose of bringing attention to the importance of the control period and of other influences which may affect the levels of blood pressure.

DISCUSSION

This study differs from that of others^{1,2} in that the control period of observation in hospital was usually considerably longer in our study (21 to 51 days). Therefore, changes in blood pressure associated with hospitalization and rest could be discounted. These changes may be great. Several additional patients selected for this regime who appeared, from previous

observations, to be suffering from moderately severe hypertension, were not studied because their blood pressures fell to normal levels in the hospital.

Although the average blood pressure levels of three of seven patients declined when they took the strict rice diet, the changes observed were not striking. While it is possible that these moderate changes were occasioned by some specific effect of this dietary regime, it is also possible that continued rest in hospital, the encouragement occasioned by a new form of therapy, or some relatively non-specific metabolic disturbance accompanying the weight loss gave rise to these results.

The blood pressure of the other four patients showed little or no response to the diet. In fact, the general condition of two of the four deteriorated. Additional hemorrhages appeared in the retinas of one, A. K., and the other, S. K., developed hypochloremia and fatal uremia. These four exhibited higher blood pressures than did the three who showed changes on the diet. Hence, they belonged to just that group for which some effective form of therapy is desirable. It is possible that the responses to the rice diet of one of the patients in each group (S. K. and L. S.) were modified by limitation of their daily intake of salt to 2 gm. during the preceding control period.

Ingestion of additional sodium chloride by two patients on the rice diet produced no consistent effect. Substitution of a normal diet for the strict rice regime caused possibly significant elevations in the diastolic pressure of only one of three patients. The inconsistencies of response observed in these few experiments prevent the drawing of definite conclusions concerning the mechanism by which the rice diet produces the beneficial effects reported by Kempner.¹

There is no doubt that the use of diets restricted as to salt will lower the blood pressure of *some* hypertensive patients. The use of these regimes only rarely achieved a maximum fall of 40 mm. Hg systolic and 30 mm. Hg diastolic,^{2,4,5} although better results have been reported on out-patients.⁶ From the past experience of one of us (H. A. S.), a rough estimate can be made that the blood pressure of only about 10 per cent of an unselected group of patients with well-established hypertension will fall to normal under the influence of a diet restricted only as to salt.⁸ Grollman and his co-workers² have also pointed this out. It is difficult to predict whether a given patient with hypertension will respond favorably to restriction of salt.

In the cases here reported, restriction of salt alone to amounts twice that in the rice diet produced changes in blood pressure in two patients which were similar to those produced by rice. In two others salt restriction or addition appeared to have a definite, although minimal effect, also comparable to those seen after use of the rice diet. Hospitalization alone caused a definite effect in three, and this added to salt restriction was effective in two others. Restriction of calories plus hospitalization affected one favorably. It should be emphasized, however, that these changes, as in the case of the rice diet, were seen, with two exceptions (W. D. and L. C.), in those patients with less severe forms of the disease. When the condition is well advanced

and necessitates some form of therapy, neither salt restriction nor the rice diet seems to be efficacious.

On the basis of this experience, it must be concluded that the rice diet is of questionable value in the treatment of most cases of hypertension, since in none of seven did striking benefits occur; indeed, the diet appeared to be harmful to one patient. It must be pointed out, however, that in only one of our seven cases (A. P.) was the diet continued for as long a period of time as was recently advocated by Kempner,⁷ although the charts published in his earlier reports¹ suggested that the response might occur fairly soon after the diet was begun. It should also be noted that the *regime* used in this study was similar to that of Kempner only as concerns dietary aspects; psychotherapeutic influences were excluded insofar as possible (patients agreeing to take the diet as an experiment with no assurance of benefit to themselves), the control period was long, and four had been restricted as to salt previously. The patients were not informed as to their progress or level of blood pressure until the conclusion of the experiments. The patients used in this study were perhaps younger than many of those indicated by Kempner in his reports.^{1,7}

It appears to us that the *regime* advocated by Kempner⁷ has at least four and possibly more factors which need evaluation: The diet is very low in protein and fat, it is very low in salt, and it has strong psychotherapeutic influences. Furthermore, control periods in hospital which we consider adequate have not been shown in his publications. Our study has attempted to evaluate only the *rice diet* itself as an influence on the level of blood pressure. Because of other factors, such as psychotherapeutic influences, the rice diet regime may well be more efficacious than the diet alone. Until advantages of this diet, which have escaped our attention, have been demonstrated, it would appear that diets merely low in salt, protein, or calories are preferable to the as yet unjustified rigors of the rice diet for use by those attempting to treat hypertension by dietary means alone.

SUMMARY AND CONCLUSIONS

1. Seven patients suffering from arterial hypertension of varying degrees of severity were treated by a diet containing unsalted rice, fruit juices and vitamins, after adequate control observations were made.
2. Diastolic blood pressures were somewhat lower in three while on the diet, but the changes were not striking. Pressures were essentially unchanged in the other four. One patient with impaired renal function developed marked hypochloremia with uremia and died.
3. The addition of sodium chloride in two cases and the substitution of a normal diet in three did not consistently reverse the effects of the rice diet.
4. Changes in blood pressure occurring in other patients after restriction of sodium chloride alone were of similar magnitude to those observed with

the use of the rice diet. Similar changes have occasionally occurred following hospitalization alone, without alterations in diet.

5. On the basis of this study, a diet of unsalted rice, fruit juices, and vitamins is of questionable value in the treatment of most patients with arterial hypertension. When the disease process was advanced, neither salt restriction nor the rice diet appeared to be efficacious.

CASE REPORTS

Case 1. L. S., a 42 year old, white, married woman, entered Barnes Hospital complaining of weakness and thoracic pain of 24 hours' duration. The onset of her hypertension occurred at the age of 29 during her second pregnancy. Hospitalization was required because of an elevated blood pressure, labor being induced in the eighth month. About a year later sugar was found in her urine, and she was placed on a low carbohydrate diet and given 20 units of insulin a day, which she continued to take for two years. Her blood pressure remained elevated continuously and was unaffected by a low-salt diet and by sedatives. In 1944, it was at a level of 200 mm. Hg systolic and 124 diastolic. Late that year, she noticed dyspnea and slight ankle edema, but this was not a troublesome complaint until August 1946, when she became confined to bed with dyspnea, orthopnea, edema, and headaches. Her urine was said then to be infected. Precordial pain appeared with radiation down the left arm, and her blood pressure was recorded as high as 270 mm. Hg systolic. She first entered Barnes Hospital because of cardiac pain in August 1946. On physical examination she was moderately obese. Her heart was enlarged, and her blood pressure was 245 mm. Hg systolic and 125 diastolic. The urine contained traces of albumin intermittently, but renal function was within normal limits. A low-salt diet did not affect her blood pressure, but she was discharged with instructions to continue taking it. Headaches and precordial pain continued, and she was readmitted on January 20, 1947, for the latter complaint. Other facts in her history were non-contributory.

On examination, the patient was markedly obese and moderately orthopneic. The arterioles in her ocular fundi were spastic and narrowed, and the veins were nicked. There were small pin-point and flame-shaped hemorrhages in both eye-grounds. The heart was moderately enlarged to the left but was otherwise not remarkable. There was pitting edema of the ankles. Blood pressure was 236 mm. Hg systolic and 124 mm. Hg diastolic.

Retrograde pyelograms were interpreted as showing either moderate bilateral hydronephrosis or large extrarenal pelves. The non-protein nitrogen of the blood was 14 mg. per 100 c.c., and renal function, as judged by the excretion of phenol-sulfonophthalein, was within normal limits. Urea clearance was 95 per cent of normal. The urine was sterile on culture. No evidence of a coronary occlusion was found.

Summary: A 42 year old woman suffered from severe arterial hypertension which was probably entering the malignant stage. Figure 1 shows the course of her blood pressure and other measurements during the ingestion of the rice diet, which was begun 21 days after admission.

Case 2. S. K. was a 56 year old, white widow who had suffered from arterial hypertension for at least nine years. She was first admitted to Barnes Hospital in May 1946, because of slight dyspnea, orthopnea and ankle edema, and because anginal pain, occipital headaches and signs of vascular insufficiency in the legs were noted. A right lumbar sympathectomy was performed, and improvement of the circulation to the homolateral leg resulted. Her blood pressure, which was at a level of 190 mm. Hg systolic and 119 diastolic, was unaffected. Because of increasing weakness, fatigue and orthopnea, without ankle edema, she was readmitted on January 8, 1947.

for study. Examination at this time showed a blood pressure of 260 mm. Hg systolic and 130 diastolic. In both ocular fundi there was tortuosity and spasm of the arterioles with a copper-wire appearance, and extreme nicking of the veins. There were numerous hemorrhages and exudates in both eyegrounds. Slight enlargement of the heart was noted. A systolic murmur was heard in the axilla, and an early diastolic murmur was audible along the left sternal border. There was marked thickening of all peripheral arteries, but there were no other remarkable findings. Her urine was sterile on culture. Blood urea nitrogen was 23 mg. per 100 c.c., and she was unable to concentrate urine to a specific gravity of more than 1.012. She was given the rice diet (figure 2).

Fourteen days later she began to complain of severe shortness of breath and prostration. She gradually lost consciousness and Cheyne-Stokes respirations developed. The white blood cell count rose to 35,400 with 94 per cent polymorphonuclear leukocytes. The rectal temperature rose to 38.6° C. The output of urine diminished markedly, varying between 40 and 270 c.c. per day during the next eight days. Plasma chlorides were found to be 69 mEq. per liter, and the non-protein nitrogen of the blood was 56 mg. per 100 c.c. The CO₂ combining power was 24.1 mEq. per liter, and the serum sodium 118.4 mEq. per liter. Subsequently, the non-protein nitrogen in the blood rose to 100 mg. per 100 c.c., although the plasma chloride concentration was elevated by the intravenous administration of 33 gm. of sodium chloride. In spite of this therapy, she died in coma, with acute uremia apparently the cause of death. Autopsy showed arteriolar nephrosclerosis, with petechiae in the renal cortices; fibrinous peritonitis and pericarditis; hypertrophy and dilatation of the heart; and general arteriosclerosis which was of an advanced degree in the abdominal aorta, coronary arteries and splenic artery.

Summary: This 57 year old woman suffered from severe hypertension in the malignant phase; she exhibited diminution of renal function without nitrogen retention. Her course on the rice diet, which terminated in death, is outlined in figure 2.

Case 3. A. K. was a 43 year old, white male who had suffered from arterial hypertension for at least one year. His only complaint was fatigue. Nine months before admission partial paralysis of his right side occurred, which slowly disappeared in a few weeks. Other than that, he was well and working as a blacksmith. The remainder of his history was non-contributory. He was admitted to Barnes Hospital on March 31, 1947. On physical examination, his systolic blood pressure was 240 mm. Hg and his diastolic 130. Aside from slight papilledema, the heart was not remarkable. In the ocular fundi there was slight papilledema, and the vessels showed some thickening without hemorrhage or exudate. His urine contained a trace of albumin and an occasional cast. The non-protein nitrogen in the blood was 20 mg. per 100 c.c. Urea clearance averaged 72 per cent of normal, and he was able to concentrate urine to a specific gravity of 1.019. Several cultures of the urine revealed *Staphylococcus aureus*. Retrograde pyelograms showed slight blunting of the calyces of the right kidney. The lowest blood pressure recorded during the sodium amyltal test was 160 mm. Hg systolic and 90 mm. diastolic.

Summary: This 43 year old man exhibited severe hypertension which was uninfluenced during his hospital stay; he was in the early malignant phase. Renal function was slightly diminished. No effect of the rice diet was seen. While he was taking the diet, fresh hemorrhages and exudate appeared in the ocular fundi.

Case 4. L. M. was a 36 year old, white male who had suffered from arterial hypertension for five years. His blood pressure was discovered to be elevated on routine examination. One year before admission, he began to notice weakness and incoördination of his left hand. Otherwise, his history was not remarkable. On physical examination, his blood pressure was 205 mm. Hg systolic and 135 diastolic. His hands and feet were cold and clammy. In his ocular fundi there was marked tor-

tuosity, narrowing and spasm of arterioles with nicking of the veins. One small area of yellow exudate was seen. Aside from slight enlargement, the heart was not remarkable. There was hyperactivity of the deep reflexes of his left arm, which showed lack of coordination. Hoffman's sign was present. There were disturbances of sensation in this extremity. The non-protein nitrogen in the blood was 15 mg. per 100 c.c. Several cultures of the urine revealed coliform organisms. The urine was not remarkable. Intravenous pyelograms revealed normal appearing renal pelvis and ureters. The urea clearance averaged 83 per cent of normal, and he was able to concentrate urine to a specific gravity of 1.026. The lowest blood pressure recorded during the sodium amytal test was 120 mm. Hg systolic and 90 mm. diastolic.

Summary: A 36 year old man had suffered permanent partial paralysis of his hand probably as a result of severe hypertension. The effect of the rice diet upon his blood pressure is seen in figure 3.

Case 5. C. O. was a 38 year old, unmarried white woman complaining of dizziness and headaches for several years. At the age of 17, she first began to have recurrent nosebleeds, and her blood pressure was found to be elevated. The nosebleeds occurred intermittently for the next five years. She also noticed occasional fainting spells, dyspnea, and headaches during the succeeding years. Prior to admission, dizzy spells, associated with headache, became more severe, and she also complained of palpitation. Examination showed a blood pressure varying between 160 and 240 mm. Hg systolic and 100 and 150 mm. diastolic. There was some excess hair in the axillae and over the extremities. Her heart was not remarkable except for a soft systolic murmur heard at the apex. The ocular fundi showed vessels which were narrowed with some nicking of the veins. She was able to concentrate urine to a specific gravity of 1.026; the clearance of urea was 71 per cent of normal. The urine contained traces of albumin; cultures of the urine showed the presence of *Staphylococcus aureus* intermittently. Intravenous pyelograms revealed no renal abnormalities. The lowest blood pressure recorded during the sodium amytal test was 100 mm. Hg systolic and 70 mm. diastolic.

Summary: This 37 year old woman had suffered from fluctuating hypertension for 20 years. There were no signs of marked damage to any organ. Headaches were unrelieved by the rice diet. Figure 4 summarizes her course.

Case 6. A. F. was 39 year old white man whose hypertension was discovered on routine examination in 1943. In 1929, he had passed a small stone *per urethram*, an episode preceded by pain in the right flank and hematuria. Headaches had appeared a year before admission but were not incapacitating. Two months before admission he again noticed hematuria and complained of aching pain in his perineum. Hematuria persisted, and he was admitted for this complaint. His blood pressure had varied from 200 to 160 mm. Hg systolic during the four years prior to entry. On examination, his systolic pressure was 200 mm. Hg and 105 diastolic. In his ocular fundi there was narrowing of the arterioles with some nicking of the veins. His heart was not remarkable, and there were no other gross abnormalities noted. Retrograde pyelograms showed a small calculus in his left renal pelvis as the only abnormality. Aside from an occasional red blood cell, his urine was not remarkable. Cultures of the urine revealed a non-hemolytic streptococcus intermittently, and on one occasion, a few colonies of *Staphylococcus aureus*. He was able to concentrate urine to a specific gravity of 1.022. Urea clearance was 117 per cent of normal. The lowest blood pressure recorded during the sodium amytal test was 118 mm. Hg systolic and 80 mm. diastolic.

Summary: This 39 year old man suffered from moderate hypertension and renal calculus. The effect of the rice diet is shown in figure 5.

Case 7. A. P. was a 42 year old, white man who was admitted to the hospital in a stuporous condition. There was no history of previous hypertension. He had complained of severe headaches for six weeks, and on the day of admission suddenly

lapsed into coma without warning. On examination, he was acutely ill, irrational, and disoriented. In the ocular fundi there were extremely narrowed arteries, with several hemorrhages and areas of exudate. The heart was slightly enlarged but was otherwise not remarkable except for a variable arrhythmia which disappeared shortly after admission. A high-pitched, blowing diastolic murmur was heard localized in the fourth left intercostal space. His systolic pressure on admission was 290 mm. Hg and diastolic 180. Neurological examination showed no signs of a localized lesion. The non-protein nitrogen in his blood was 26 mg. per cent. There was marked albuminuria with a few red blood cells in the centrifuged sediment. During the first week he exhibited low-grade fever. His blood pressure remained at the same levels as on admission. The non-protein nitrogen in his blood became elevated to 91 mg. per cent. The patient slowly recovered from his stuporous condition during the next week or 10 days and the non-protein nitrogen level of his blood gradually returned to normal during a month's time. The urea clearance was 33 per cent of normal. After a month in the hospital, he was asymptomatic although the level of his blood pressure had not changed appreciably, his diastolic varying between 180 and 160 mm. Hg. He was placed on the rice diet for a period of three months without effect on his blood pressure. At the end of this time, the urea clearance was 15 per cent of normal, and there was only a trace of albumin in the urine.

Summary: Fulminating hypertension with renal impairment in a 42 year old man whose first symptom was an attack of encephalopathy. His course on the rice diet, which did not affect the level of his diastolic pressure, is shown in figure 6.

Case 8. L. C. was a 33 year old, unmarried, colored woman who was first found to have arterial hypertension at the age of 27, when she suffered a severe nosebleed. She had no complaints until 14 months before admission when an episode of dyspnea, blurring of vision, dizziness, and ankle edema occurred. Eleven months before this study (November 1946) she had been admitted to this hospital because of a sub-arachnoid hemorrhage, the signs of which cleared slowly. Her blood pressure on a low-salt diet fell from a level of 200 mm. Hg systolic and 130 diastolic to normal levels, the lowest point being 110 mm. Hg systolic and 70 diastolic. Her weight at that time was about 300 pounds. Ever since puberty she had noted an excess of hair on her chin and chest, and it was necessary for her to shave her face about twice a week. Obesity, difficult to control, had been present since then. Although the classical findings of Cushing's syndrome were absent, obesity of the trunk and face and hirsutism were highly suggestive. At the time of admission she had no complaints.

On physical examination, she was markedly obese, with the obesity confined to the trunk, thighs, upper arms, and face. There was a well-developed beard on the chin and a slight mustache. There were pale striae about the arms, back, buttocks, and thighs. There were no hemorrhages or exudates in the ocular fundi, although the arterioles were markedly thickened with irregular areas of constriction. The margins of the optic discs were blurred. Except for a loud, harsh, low-pitched, systolic murmur heard over the precordium and some enlargement, the heart was not remarkable. Laboratory findings were non-contributory; she was able to concentrate urine to a specific gravity of 1.026, and the clearance of urea was 139 per cent of normal. Glucose tolerance test was normal, and no excess 17-ketosteroids were found in her urine, the amount being 3.3 mg. in 24 hours. She excreted 13 mg. of sodium pregnanediol glucuronide in 24 hours.* The urine was remarkable in that it never contained albumin or abnormal microscopic elements in repeated examinations.

Summary: This 33 year old woman suffered from marked obesity, hirsutism, and severe arterial hypertension for six years. Her blood pressure appeared to respond to variations in the intake of sodium chloride, as seen in figure 7.

Case 9. W. D. was a 42 year old, white, married railroad worker, whose blood pressure was found elevated one year previously. His complaints consisted of fatigue,

* Determinations made by Dr. W. M. Allen.

mild exertional dyspnea, and one attack of weakness of his right side which gradually improved during several weeks. He also complained of severe occipital headaches and transient numbness in his right hand and arm.

On examination, the ocular fundi revealed marked narrowing of the arterioles without hemorrhage, exudate or papilledema. There was slight cardiac enlargement. Neurological examination showed hyperactive deep reflexes on the right. His clearance of urea was 87 per cent of normal, and he was able to concentrate urine to a specific gravity of 1.021. There was moderate albuminuria without abnormal microscopic elements. The average plasma clearance of para-amino hippurate was 360 c.c. per minute, and of mannitol 96.5. Albuminuria disappeared during his stay in the hospital.

Summary: A 42 year old man with arterial hypertension of at least one year's duration, who showed only slight diminution of renal function. His blood pressure appeared to be lowered by restriction of salt (figure 8).

Case 10. F. W. was a 23 year old, white, unmarried woman whose blood pressure was found elevated only three months previously. She had been complaining of headaches and increasing nervousness for five years. On one occasion, six months before admission, she had noticed choking sensations and shortness of breath lasting several hours. This recurred two months later. She had also noticed swelling of her ankles. On examination, she was moderately obese. There was some thickening of the arterioles in the ocular fundi with no hemorrhage or exudate. There was slight enlargement of her heart; otherwise, the examination was not remarkable. There was no albuminuria, although she was able to concentrate urine to a specific gravity of only 1.016. The clearance of urea was 48 per cent of normal. There were no abnormal findings on intravenous urography. It was noted that a typical "dienecephalic" blush appeared on embarrassment or emotion, associated with severe spells of crying and emotional outbursts.

Summary: A 23 year old woman suffered from arterial hypertension with diminution of renal function. Her diastolic pressure was not lowered by restriction of salt (table 1).

Case 11. I. H. was a 43 year old, white, married woman who had had known hypertension for 11 years which apparently developed in the seventh month of her first pregnancy, associated with toxemia. Two years later another pregnancy was interrupted because of severe hypertension and vomiting. She had no symptoms until three years before admission, when occasional right sided occipital headaches, dizziness, palpitation, fatigue and dyspnea on exertion appeared. Several episodes of dizziness and blurred vision and headache in the interim made her most uncomfortable. She had been obese for many years. She had been followed in the Washington University Clinics where her blood pressure ranged from 198 to 238 mm. Hg systolic and 120 to 140 diastolic. On physical examination, she was very obese with the obesity most marked in the trunk and proximal parts of the extremities. In her ocular fundi were irregularities in caliber of the arterioles without hemorrhage or exudate. Her heart was slightly enlarged but otherwise was not remarkable. There were no other findings of note. In her urine was a moderate amount of albumin with a few red blood cells in the centrifuged sediment. She was able to concentrate urine to a specific gravity of 1.023, and her clearance of urea was only 55 per cent of normal. On admission, she was placed on a diet containing 2 gm. of sodium chloride, following which her blood pressure fell at times to normal levels. When her intake of sodium chloride was raised to 12 gm. per day, her blood pressure became more elevated; later restriction of salt was followed by a fall in her systolic pressure to 130 mm. Hg and her diastolic to 80.

Summary: This 40 year old woman had suffered from arterial hypertension for 11 years, beginning apparently with a toxemia of pregnancy. She was also obese.

The addition of salt to her diet appeared to raise the average level of her blood pressure slightly, and a subsequent withdrawal seemed to lower it (table 1).

Case 12. D. B. was a 28 year old, white, married woman complaining of fatigue, fullness in her head, and flushing of the face, hands and arms. Her first admission was in 1944 because of hypertension, discovered at the age of 23. Her blood pressure then was 172 mm. Hg systolic and 118 diastolic, and there were no signs of damage to any organ or system. Her blood pressure was noted to be quite labile during her stay. She was readmitted in 1946 when albuminuria was first noted. At that time, there had been a decline in the ability of her kidneys to concentrate urine to more than a specific gravity of 1.023, and her clearance of urea was 66 per cent of normal. A lumbar sympathectomy was performed which only temporarily influenced the level of her blood pressure. Her third admission was in June 1947 for unexplained fever. At that time, there were few changes in her renal function and none in the level of her blood pressure which remained elevated. She was readmitted in February 1948 for study. On examination, there were no remarkable findings. The ocular fundi showed arterioles only slightly thickened. During the examination, a blotchy erythema appeared over the arms, face and chest which was typical of the "diencephalic" blush. There was no albuminuria, and she was able to concentrate urine to a specific gravity of only 1.020. The clearance of urea was 104 per cent of normal. Glucose tolerance test was not abnormal. Her renal plasma flow, using para-amino hippurate, was 485 c.c. per minute and mannitol clearance was 109. These figures were essentially normal for her size. Her blood pressure was quite labile, and the "diencephalic" blush appeared at frequent intervals during examinations.

Summary: This 28 year old woman suffered from arterial hypertension of the "neurogenic" type for five years without damage to any system. Lumbar sympathectomy had not influenced the level of her blood pressure, which did, however, fall somewhat after three months' hospitalization (figure 9).

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RHEUMATOID SPONDYLITIS: OBSERVATIONS ON THE INCIDENCE AND RESPONSE TO THERAPY AMONG VETERANS OF THE RECENT WAR*

By ELAM C. TOONE, JR., M.D., *Richmond, Virginia*

THIS report deals with a series of 29 cases of rheumatoid spondylitis observed over a period of 15 months on the wards of a General Veterans Administration Hospital. Reports by several writers^{1,2} have indicated that this disease has occurred among service personnel in a relatively greater ratio to peripheral rheumatoid arthritis than has been observed among the civilian population. Nevertheless we were not prepared for the number of cases encountered at a hospital not designated especially for the care of joint diseases. During the period under consideration there were 8,937 admissions to the hospital as a whole and 197 admissions to the wards set aside for the care of arthritic patients.

CONTRIBUTORY FACTORS

Age: The average age on admission was 27.75 years with the youngest patient 21 years of age and the oldest 48 years. The average age at the onset of symptoms was 22.33 years with a range of from 10 to 30 years. *Sex:* There were 29 males and 0 females. This ratio is to be anticipated in a veterans hospital, but it should be mentioned that the number of female patients encountered in such institutions is greater than one would expect. *Race:* There were 26 white and three negro patients.

Exposure and Infection: Twenty-three cases were considered to be service connected, five cases developed the disease before entering the armed services, and in one case the service connection was undetermined. There were 25 who had been in the Army and four in the Navy. Four cases were precipitated by combat experiences and one while training for combat. Only four patients stated that symptoms began during periods of unusual exposure to cold and wet weather and none gave a history of any significant infection immediately preceding or occurring coincidentally with the onset of the disease.

Trauma: Eleven patients related trauma to their disability but in none was this of a severe or unusual nature. Two patients had falls of from 8 to 10 feet, one patient accused a lumbar puncture, another struck his back when wrestling, but in the remaining seven nothing more than the lifting and

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bending associated with the routine duties of a mechanic, munitions carrier or stevedore could be found.

Geographical Factor: For the most part rheumatic diseases have been associated with the temperate zones and cold wet weather recognized as a distinct contributing factor. In this group, however, 10 of the cases described their symptoms as beginning while they were stationed in the tropics or subtropics. Three were located in Hawaii, one in Panama and the others scattered about the South or Southwestern Pacific in such places as the Fiji or Sovereign Islands, New Caledonia or Guadalcanal. All of these regions were warm or hot, but had in common a heavy rainfall and were prone to be damp and cool at night. Fifteen cases noted the onset of symptoms within the United States in areas ranging from Georgia to Washington state and from Louisiana to Illinois. One patient developed the disease while on duty in the desert region of Southern California. In one instance the disease began in Iceland and in another while in Germany.

SYMPTOMATOLOGY

Pain and Stiffness: Pain is the universal complaint of patients with rheumatoid spondylitis and so was found to be the major complaint in each of the patients of this series. At the onset the pain is usually localized to the lower back, is often sharp and stabbing in character, intermittent in occurrence and tending to be more severe at night. Occasionally it may radiate into the lower extremities along the course of the sciatic nerves or around the lower trunk or chest. As the disease progresses the pain becomes more constant and severe with the patient noting progressive stiffness first of the lower back and later of the entire spine with the hips or shoulders often involved. As the stiffness progresses the pain frequently diminishes in intensity although a dull aching discomfort usually persists and acute exacerbations of pain due to minor stresses and strains are frequent.

Secondary symptoms such as insomnia, anorexia, and weight loss are common. The average weight loss in this group was 18 pounds with variation from no loss to a loss of 46 pounds. Discouragement, frustration, and severe mental depression were frequently encountered and one patient attempted suicide by drinking lye, which succeeded in complicating his already difficult illness with a severe esophageal stricture.

Mode of Onset: The gradual and intermittent development of the symptoms in the early course of the disease leads to many difficulties in early diagnosis and consequently a delay in early treatment. In 23 cases the onset was of a gradual nature and in six abrupt. This circumstance, as much as any other, contributes to the difficulties in early diagnosis so that at the time of admission to the hospital the average duration of the symptoms was 58 months. Almost all of the patients felt discouraged and confused by multiple varied diagnoses and inappropriate and ineffective management. Only two patients had previously received roentgen-ray therapy.

Sequence of Joints Involved: Although the disease is primarily an involvement of the articulating surfaces of the spine, it must be recognized that occasionally it may begin in other joints. Twenty patients first noted symptoms in the lower back, five in the hips, two in the ankles and knees and one in the sternoclavicular joints.

PHYSICAL EXAMINATION

General Appearance, Posture and Gait: The average patient has a tall slender physique and often shows evidence of moderate weight loss. On gross inspection the posture frequently appears unaltered, but on close examination of the back certain changes can be detected. There is a loss of the lumbar curve in most instances with definite spasm of the paravertebral muscle groups. Movement of the back in all directions is guarded and restricted and when attempting forward flexion the lumbar spine remains rigid and flat. More advanced cases show evidence of dorsal kyphosis, scoliosis, a tilted pelvis or a "frozen" depressed shoulder. The gait is always abnormal. The back is held rigid in walking and the patient constantly guards against motion in any direction. If the disease is extensive the neck is likewise restricted in motion and the entire body must be turned in looking from side to side. With involvement of the hips the gait becomes even more disturbed, and with ankylosis of the hips the patient is apt to become a complete economic loss.

Impaired Motion: Involvement of the sacro-iliac and apophyseal joints alters and restricts motion of the spine in all directions although this is most strikingly demonstrated in attempts at forward flexion. The average patient was able to reach to only within sixteen and one-quarter (16.25) inches (40.8 cm.) of the floor with a range of from 5.5 inches (14.03 cm.) to 24 inches (61.2 cm.). Involvement of the costo-vertebral joints reduces the excursion of the thoracic cage and the average chest expansion was 1.5 inches (3.83 cm.) with variations of from .25 to 3 inches (.64 to 7.65 cm.).

Joints Involved: Thirteen cases showed involvement of the spine alone, in 12 cases the spine, hips and shoulders were affected, and in four patients the spine, hips, shoulders and multiple peripheral joints.

LABORATORY STUDIES

There are no laboratory findings of a pathognomonic nature associated with this disease. Some few are of value as an aid to diagnosis, but for the most part studies of the blood, urine, spinal fluid, and blood chemistries are normal or have no positive diagnostic value.

Sedimentation Rate: This is probably the most helpful of all laboratory studies and is almost always increased. The average rate (Cutler) in this group was 26 mm. with variations of from 7 to 40 mm.

Vital Lung Capacity: Because of the reduced expansion of the thoracic cage and limited chest expansion this, as would be expected, is reduced. In

27 cases this averaged 72.3 per cent with a range from 50 per cent to 109 per cent of normal.

Hemoglobin: The average hemoglobin determination on admission was 13.5 grams with a range from 11 grams to 15.5 grams.

Acid Phosphatase: In five cases in which this examination was made the acid phosphatase was normal.

ROENTGEN EXAMINATION

Roentgenographic changes are probably the most valuable single finding in the diagnosis of rheumatoid spondylitis. These changes are noted most often in the following areas:

Sacro-Iliac Joints: These are the most important joints to be examined and will almost always show a bilateral involvement³ if the disease is present. This may vary from an early narrowing of the joint space with irregular bone proliferation and osteoporosis of the adjacent bone to complete ankylosis. Each of the 29 cases in this series showed bilateral involvement of these joints.

Apophyseal Joints: These joints are more difficult to visualize and special oblique views are necessary to demonstrate any change. Here again changes vary from narrowing of the joint space to complete ankylosis. Examination of these joints was used only rarely in this series of cases and could not be said to have done more than add confirmatory evidence.

Spinal Ligaments: Calcification of the anterior and lateral ligaments and of the ligamentum flavum is a common finding and may appear relatively early in the disease. Fifteen cases showed evidence of calcification in one or more of these ligaments.

TREATMENT

Treatment of this disease is directed to the following objectives: (1) The general care of the patient, (2) the relief of pain, (3) the prevention of spinal deformities.⁴

General Care of the Patient: Since there is no specific therapeutic approach, measures are necessary to enable the patient's own natural resistance to combat the lesion. These measures consist of adequate rest and a high caloric diet supplemented with vitamins. Of equal importance is the necessity of quieting the patient's apprehension about himself and his disease and restoring his morale. This is accomplished by a simple explanation of the nature of the disease and a prognosis couched in as optimistic fashion as the circumstances allow.

The Relief of Pain: At the present time the use of a penetrating roentgen ray (190 K. V.) directed over the back has proved to be the most effective measure in controlling the pain in rheumatoid spondylitis. Almost from the time of the discovery of the roentgen-ray this form of treatment has been used in a variety of modifications.^{5, 6, 7} The technic generally used today,

however, is that advocated by Smyth, Freyberg, and Lampe in 1941.* This consists of dividing the spine into four areas and giving a total of 600 R in three to four doses at intervals of from two to four days. The schedule of treatment is so arranged that alternate areas are treated at the same time.

In the cases reported here the technic which has been employed is outlined in table 1. Treatments are given at biweekly intervals for two weeks until each area selected for treatment has received 600 R and the patient is allowed a rest interval of from six to eight weeks and the course is repeated. The average patient receives a total of three courses in this manner and then further treatment is withheld for six months unless a relapse occurs. At the end of six months the patient returns for reevaluation and treatment is repeated or withheld according to his response.

The mode of action of roentgen-rays in relieving pain in rheumatoid spondylitis is not understood, but apparently its greatest beneficial effect results from its ability to lessen muscle spasm.

TABLE I
Treatment Technic

1. Spine or back in four areas.
 1. Sacro-iliac 20×20
 2. Lumbar 10×15
 3. Dorsal 10×15
 4. Cervical 10×10
2. K.V. 190 M.A. 20 T.S.D. 50 cm.
.5 mm. copper —Filter
1.0 mm. aluminum
3. Dose: $150 \text{ R} \times 4 = 600 \text{ R}$.
1 course per area.

Reaction to roentgen-ray therapy is fairly common and 75 per cent of our patients noted nausea, anorexia, or general malaise in varying degrees during treatment. In no instance was this of serious consequence and in no case prevented the completion of the full course of therapy. In one case not included in this series the leukocyte count dropped sufficiently low to warrant discontinuing treatment.

Other measures used to control pain are the free use of analgesics such as acetylsalicylic acid, phenacetin or sodium salicylate. In no case was it found necessary to resort to the use of a narcotic.

Correcting Deformities: The importance of a proper posture is stressed and all patients are instructed in exercises designed to maintain a normal posture and to strengthen the back muscles. Deep breathing exercises are given three times daily to increase the excursion of the thoracic cage. Since much of the early treatment of rheumatoid spondylitis is carried out with the patient confined to bed, it is important that his back be strengthened and supported during this period. This is best accomplished by the use of a

thin cotton or felt mattress supported on fracture boards which must extend under the entire length and width of the mattress. Only a small pillow should support the head. For 30 minutes each day the patient lies with a small pillow or sandbag under the lower dorsal area in order to hyperextend the spine.

An attempt is made to dispense with the use of any artificial type of support unless necessary to control a progressing deformity or to control pain not satisfactorily relieved by roentgen-ray therapy. If a support is necessary, the Taylor back brace or a "Three Point Brace" ⁴ utilizing a rectangular support across the sternum are the types most often used. Frequently a simple sacro-iliac belt is sufficient to control persistent low back pain. The use of traction in hip involvement with severe muscle spasm was a very useful procedure in two cases and the use of manual manipulation followed by the application of a cast served to establish a wider range of motion in one case with a "fixed" shoulder.

THE RESULTS OF TREATMENT

Twenty-eight patients were treated with roentgen therapy.

Relief of Pain: Nineteen cases (67.9 per cent) reported a definite relief of pain and were improved by the treatment. In seven of these the results were excellent with no discomfort while at rest or on moderate use of the back. Statements to this effect were further qualified by the fact that sleep was uninterrupted and that analgesics and back supports could be dispensed with. Twelve patients reported a substantial relief of pain and were classified as good results. In these there was slight residual discomfort, sleep was occasionally interrupted and the patient still relied to some degree on analgesics and back supports or braces.

Nine cases reported no relief of pain or relief of such a minor degree as to be classified as unimproved.

Any attempt to evaluate a symptomatic response to treatment is difficult. There has been reason to believe that improvement has been definite in the cases cited because of the high incidence of returns for the completion of the treatment schedule. Each patient is discharged to his home between courses and in some instances this amounted to travelling from 500 to 700 miles. Nineteen patients have returned for two or more series of therapy; two receiving four courses, 10 receiving three, and seven receiving two.

Other Results: It has been emphasized by others ^{6,7} that whereas roentgen-ray therapy is a valuable agent in relieving pain, it has not been of value in directly affecting the cause of the disease or of arresting the pathologic process. Some writers ⁷ have noted an improvement in the sedimentation rate although this has not been our experience to any striking degree. The average sedimentation rate on admission was 26.0 mm. and at the time of discharge 23.1 mm. Probably as a result of the relief of pain associated with an improvement in appetite and uninterrupted sleep there was a slight aver-

age weight gain with an increase from 143.75 lbs. on admission to 150.75 at the time of discharge. So far as the relief of stiffness is concerned the results are not impressive. This applies to the thoracic cage as well as to the spine proper. On admission the average range of flexibility was to within 16.25 inches (40.8 cm.) of the floor and at discharge to within 15 inches (38.25 cm.). The average chest expansion on admission was 1.5 inches (3.83 cm.) and remained unchanged after treatment. The average vital lung capacity before treatment was 72.3 per cent and after treatment 73.1 per cent.

SUMMARY

Rheumatoid spondylitis is a disease of unknown etiology capable of producing severe crippling deformities and is particularly prone to affect otherwise healthy young males. Information gained from these observations and from reports published elsewhere indicate that its incidence is increasing. Precipitating factors such as trauma, exposure, infection and climatic conditions are variable and inconstant and knowledge about the cause and pathogenesis of the disease is inadequate. Roentgen therapy is a valuable means of controlling pain and relieving muscle spasm, but must be combined with measures of a general supportive nature and with measures designed to prevent or correct deformities. This plan of treatment appears as the most satisfactory available at the present time.

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DIABETIC INDIGESTION *

By ANTHONY BASSLER, M.D., F.A.C.P., LL.D., and A. GERARD PETERS, M.D., *New York, N. Y.*

DYSPEPTIC symptoms occur at times in diabetic patients and are related to the lack of control of the diabetes. We have seen a number of patients complaining of indigestion who, on examination, have shown only glycosuria and hyperglycemia to be present. Some of these patients were known diabetics, who at the time of examination were poorly controlled, others had never been diagnosed as having diabetes mellitus. The symptom encountered most commonly in these patients was a true pain in the epigastric region or across the upper abdomen. It varies in severity, sometimes being only a pronounced distress, but it is usually continuous and independent of meals. It is only slightly relieved by alkalis or sedatives. With severe acidosis, the clinical picture may simulate that of an acute surgical abdomen, which is not suggested in what we have designated as a diabetic indigestion. Other complaints encountered in these simple indigestion cases include post-meal distress consisting of pyrosis, bloating, belching and fluid regurgitation. Usually the appetite is good. Thirst is not complained of because polyuria is not present or pronounced enough to be noticed. The purpose of this paper is to present a description of a subjective type of indigestion in an individual who has a mild grade of diabetes mellitus and the dramatic result on the digestive symptoms of treatment directed toward the diabetes.

The Abdomen in Diabetes. The evaluation of abdominal complaints in the presence of diabetes mellitus must be circumspect, because for reasons which are still obscure, they occasionally differ from similar complaints in the non-diabetic. Abdominal complaints occurring in a diabetic person may be conveniently classified into three broad groups:

1. *The Acute Abdomen of Diabetic Acidosis.* A diabetic patient in acidosis may present the clinical picture of an acute abdomen. Bothe and Beardwood¹ reported a series of 136 cases of diabetic acidosis in which 96, or 74 per cent, presented the abdominal symptoms of nausea, vomiting and abdominal pain, usually associated with leukocytosis and fever. In the same series the remaining 26 per cent had central nervous system symptoms of drowsiness and coma. The abdominal symptoms rapidly disappear when the acidosis has been overcome.

2. *Organic Diseases of the Abdomen Occurring in a Diabetic.* In general, the clinical picture and laboratory findings in this group are similar to like conditions occurring in other patients. However, some observations should be noted. Acute abdominal infections may not produce as severe

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symptoms in diabetics as in non-diabetics under similar conditions. Severe abdominal infections may occur in diabetics without the presence of acidosis. Elsewhere in the body, infections occurring in diabetics are usually associated with an acidosis.

Stomach. Almost one-third of a series of 399 diabetics had a complete anacidity.² The incidence of peptic ulcer in a series of 12,000 diabetics was 94 cases or only 0.98 per cent.² In over half of these the typical ulcer syndrome was absent. In only 12 per cent was the HCl over 40° and in 67 per cent there was either no free HCl or it was below 20°. Severe complications of peptic ulcer in diabetes are unusually frequent. In the series cited above, massive hemorrhage occurred in 26.6 per cent, obstruction in 34 per cent and perforation in 10 per cent. Gastric carcinoma occurs somewhat more often than in non-diabetic ulcer patients.

Liver. Hepatic enlargement has been noted in patients with diabetes.³ The diabetic is prone to fatty infiltration of the liver³ and to depletion of the liver glycogen.³ Diabetes is associated, frequently, with disease of the liver as evidenced by the presence of a strongly positive colloidal gold reaction. Hepatic involvement is much more prevalent in severe than in mild diabetes.⁴

Gall-Bladder. Diseases of the gall-bladder occur more commonly in the diabetic than in the general population and about one in four diabetics have gall stones at autopsy.

Pancreas. Impaired external secretion of the pancreas may be found in diabetics with diarrhea. However, in most diabetics digestion and absorption of foods seems to take place normally.⁶

3. *Diabetic Indigestion.* These patients usually have a mild diabetes which is either not diagnosed or is poorly controlled. Acidosis is usually absent. Their complaints of abdominal symptoms and digestive disturbances are prolonged in character and are rapidly relieved by proper control of the diabetes. As previously mentioned their complaints include: Upper abdominal pain, pyrosis, bloating, belching and fluid regurgitation following meals.

This last group is the one with which we are particularly concerned. Often the patient has been subjected to exhaustive laboratory studies to determine the reason for the complaints and little concern has been evidenced over a mild glycosuria and a slightly elevated blood sugar with no acidosis. Yet, when the diabetic situation has been better controlled, by diet alone or by diet plus insulin, the digestive disturbances disappear. No satisfactory explanation of this phenomenon has been advanced to date. Why some diabetic patients should have digestive complaints while others do not is difficult to explain, as are acute abdominal symptoms seen in diabetic acidosis. The severity of these digestive disturbances does not seem to be related to the severity of the diabetes.

The following case reports illustrate the condition above described as diabetic indigestion.

CASE REPORTS

Case 1. A 61 year executive, first seen in 1946, had complained of indigestion, consisting of constant epigastric distress unrelated to food for about one and one-half years. He also had intermittent attacks of colicky epigastric pain which on two occasions necessitated opiates by hypodermic. The clinical diagnosis of biliary colic due to stones was made. These attacks of pain occurred at about three month intervals. His last attack had occurred about one month before he was seen. He had been hospitalized at that time and the physical examination was reported to be unremarkable except for moderate epigastric tenderness. The urine was reported as normal. An electrocardiogram was normal. After his ingestion of opaque dye, the gall-bladder was not visualized nor were any calculi evident. He was advised to have his gall-bladder removed. When seen by us one month later he still complained of epigastric distress but no severe pain. Physical examination was normal. Blood pressure 146 mm. of mercury systolic and 86 diastolic. There was a glycosuria with no acetone bodies. Fasting blood sugar was 162 mg. per cent. With diet alone the blood sugar level came down to 112 mg. per cent and the glycosuria disappeared in about three weeks. During the second week of treatment all symptoms of pain and indigestion gradually disappeared and have not recurred for a year to date. It is possible that this patient had a diseased gall-bladder, but it was not responsible for his symptoms.

Case 2. A 75 year old female had been a patient for 32 years. At the age of 28 she had an ovary and an intramural uterine fibroid removed. She continued to menstruate for six years and went into the menopause at 34. At 38 she had a cholecystectomy for gall stones. Since then she had occasional attacks of indigestion consisting of colicky pains, pyrosis, regurgitation of acid fluid from her stomach and also constipation. She was seen at irregular intervals for minor complaints. Her urine was always negative for glucose. She was not seen during the years 1929 to 1944. In 1944 she complained of swollen, reddened and itching vulva. Her urine was positive for glucose, no acetone was present and her fasting blood sugar was 189 mg. per cent. She did not complain of indigestion at this time and stated that she had been free of it for a number of years. With a moderately restricted carbohydrate intake and low fat diet plus 10 units of insulin per day, the vulvar condition rapidly cleared. Being satisfied with her improvement and general state of health, she became careless about her diet. Some six months later, indigestion occurred, beginning one evening with an acute attack of pain in the upper abdomen, slight fever (101° F.) and a leukocyte count of 14,200. The differential count was not especially significant. The physician in charge diagnosed her condition as an acute cholangitis and advised operation. She was brought to New York City at which time she complained of indigestion and a continued pain in the upper abdomen. Her temperature and blood count were normal. There was glycosuria and the ferric chloride and sodium nitroprusside tests were positive. The fasting blood sugar was 210 mg. per cent. After a complete examination, no cause for the abdominal complaints could be discovered. With insulin and diet her urine cleared and her fasting blood sugar came down to 130. She was placed on a diabetic regimen plus 40 units of protamine zinc insulin. What is interesting is that as the diabetes was controlled, the sedatives and opiates could be dispensed with, and the pain and indigestion disappeared. She has now been free of digestive complaints and abdominal pain for two years.

Case 3. A banker, 38 years of age, had an appendectomy in 1931. Because of an attack of jaundice in 1941 he had his gall-bladder x-rayed and was told it was diseased. A month later it was reexamined and he was told that he had a "sluggish gall-bladder." He stated that he was all right if he restricted sugars and starches in his diet. When he went into the Army, he ate everything and had only one attack of pain which was promptly relieved by an injection. In February 1947 he began to

have epigastric pain, usually occurring in the late afternoon and accompanied by a sensation of pressure in the upper abdomen. He stated, "I have a big appetite, am thirsty and pass more urine than in previous years and have some insomnia recently." Although he had several urine examinations in the past, the presence of glucose had never been mentioned. At the time of examination in May 1947 there was glycosuria with no acetone bodies. Fasting blood sugar was 150 mg. per cent. With diet alone his blood sugar gradually came down to 90 mg. per cent and the urine was sugar-free. For the past six months he has felt well and has had no abdominal complaints.

Case 4. M. P., a 58 year old male truck driver with a non-contributory past history, began complaining of upper abdominal pain in 1946. At times the pain was severe but it had no relationship to meals or type of food. He had been diagnosed as having a peptic ulcer. Under treatment the pain persisted continuously for 10 months. He stated that he was fatigued and "too weak to work." He had insomnia and occasional attacks of diplopia. He "loves sweets," had a good appetite and lately passed a "good deal of urine." He was about 26 pounds overweight. His blood pressure was 150 mm. of mercury systolic and 86 mm. diastolic. General physical examination was negative. There was glycosuria with no acetone bodies. Fasting blood sugar was 170 mg. per cent. With diet plus 20 units of protamine insulin a day the diabetes was easily controlled and he began to feel much better. As the symptoms of diabetes disappeared, his digestive complaints abated. For over a year, with moderate increase in carbohydrate and 20 units of protamin insulin, he has had no indigestion and has been working steadily.

Case 5. A man of 74 was referred by Dr. Bejak of New York in June 1946. Six months before he suddenly got a "tremendous" pain in the abdomen, which a physician in the country where he lived said was due "to a cold in the kidneys." This pain, while less intense, had never disappeared since it started. He described it as a pulling sensation across his upper abdomen especially in the "pit" of his stomach. He had no other abdominal symptoms. His general condition was good except for a moderate hypertension (blood pressure 190/90). The urine contained glucose and a trace of albumin. The fasting blood sugar was 183 mg. per cent. The gall-bladder was static, retaining the dye over 48 hours. No stones were visualized. A moderately spastic colon was also noted. Being about 20 pounds overweight, hypertensive and diabetic, he was placed on a low fat diet with restricted carbohydrates. In a week he lost four pounds but glycosuria persisted. He was given 20 units of insulin a day and at the end of the third week he had lost 10 pounds, the urine was negative for both glucose and albumin and there was a reduction in the systolic blood pressure of 20 mm. of mercury. The abdominal pain disappeared four days after insulin was begun. The patient was seen one and a half years after initiating treatment for the diabetes and he states, "he feels perfectly fine in every way."

COMMENT

All of these cases illustrate one important point, namely, proper control of the diabetes also controlled the digestive complaints. In a patient with abdominal complaints of a digestive nature in whom glycosuria is discovered, it is well to postpone evaluation of the abdominal situation. Attention should be directed toward accurate diagnosis and adequate treatment of the diabetes. When the diabetes is well controlled, in more than half of the cases we have seen, the digestive disturbances have disappeared completely. With persistence of the original complaint, a further investigation should be conducted to discover the cause of the indigestion. Another point which

should not need to be emphasized is that every patient who complains of digestive disturbances should have a urinalysis. As Joslin² puts it "don't depend on symptoms for diabetes. Diabetes will not be found without search." Some obscure abdominal complaints are caused by diabetes and are readily amenable to its treatment.

SUMMARY

Digestive disturbances, relatively mild in nature but present over long periods of time are occasionally encountered in mild cases of diabetes.

Often the underlying diabetic state is not discovered or considered significant and the patient presents a puzzling picture.

The condition which we have presented as diabetic indigestion does not appear to be due to an acidosis or to any organic condition. Treatment directed toward proper control of the diabetes rapidly relieves the patient of all digestive disorders. If symptoms persist after the diabetes is controlled, search elsewhere for the cause of the indigestion is in order.

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SOME UNUSUAL OBSERVATIONS IN POST TRANSFUSION REACTIONS: TWO CASES WITH AUTOPSY FINDINGS*

By VICTOR A. DIGILIO, M.D., and ADOLF HOCHWALD, M.D.,
Philadelphia, Pennsylvania

THE renal pathologic lesion following hemolysis of transfused blood has been described many times (Bordley,¹ Goldring and Graef²; DeGowin, Warner and Randall³; Dardinski⁴; Payne⁵; Witts,⁶ among others). Lesions of other viscera have also been observed, but reported less frequently (Bordley, Goldring and Graef; Dardinski).

The relationship of intravascular hemolysis to the resulting renal disease and lesions of other viscera does not appear to be clear. Indeed, some difference of opinion still exists relative to the pathogenesis of the so-called transfusion kidney.³

The two cases to be reported herein because of marked differences in the duration of life after the transfusion time-interval before death, yet with practically identical necropsy findings, may permit certain deductions.

CASE REPORTS

Case 1. Mrs. V. T., a white woman of 32, was admitted to the Woman's Medical College Hospital on July 8, 1943. The presence of fever, joint swelling and pain, leukopenia, palpable liver and spleen, and the development of skin lesions over the forehead and "butterfly" area, were indications of acute lupus erythematosus. This was confirmed by the dermatologist, who suggested, among other things, repeated small blood transfusions.

On the evening of July 20, 250 c.c. of blood were administered over a period of one and one-half hours. At the end of this time, the patient had severe chills, vomiting, incontinence of urine, and a rise in temperature to 105.4°. She felt improved after 3 minims of adrenalin. There was slight cyanosis but no pitting edema.

At 1:30 a.m., July 21, the patient began to vomit and seemed in critical condition. She was staring blindly into space with pin-point, non-reactive pupils. She responded only by a flicker of her eyelids to her name, and began to have bilateral convulsive movements. Her pulse was imperceptible at the wrist, blood pressure was 60 mm. Hg systolic and 26 mm. diastolic, respirations very labored and occasionally almost Cheyne-Stokes in character. Shock treatment was given—plasma, cortin, shock blocks, and 1000 c.c. sodium lactate (slowly, by vein). Blood pressure rose to 84 mm. Hg systolic and 50 mm. diastolic, the pulse and respirations improved, but the patient remained entirely unresponsive. About 6:20 a.m., blood pressure 90 mm. Hg systolic and 40 mm. diastolic, and 3 c.c. of cortin were given intravenously, during which respirations ceased. Patient responded briefly to coramine and metrazol, but died at 6:50 a.m. Death occurred about 12 hours after transfusion. (Laboratory data table 1.)

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From the Departments of Medicine and Pathology of the Woman's Medical College, Philadelphia, Pa.

Autopsy Findings: Gross Description: General: Body is that of an obese white woman about 35. Lips and nails are blue. Skin is yellow; sclerae are clear. Breasts appear normal. There are the following lesions in the skin: (1) On cheeks and bridge of nose dusky red, fairly well demarcated areas of edema, larger on right cheek. (2) On midforehead at hairline is a reddish area which centrally is covered with fine dry scales, similar lesions on neck. (3) Small dull red papules on trunk and arms, larger ones on legs showing small ulcers. (4) Small blue linear scar on right scapula. (5) Slightly depressed circular scars below right clavicle, on sternum and in lumbar region. (6) Hair, especially in occipital region, and skin of neck covered with greasy scales. Diaphragm: left dome at fourth interspace; right at third interspace. Serous cavities: *Pericardial* cavity is normal. *Pleural* cavities: left appears normal, right contains about 300 c.c. of clear fluid; there are scattered fibrous adhesions on lower lobe. *Peritoneal* cavity: there is no dilatation of vessels in splanchnic area; no fluid in cavity. *Aorta*: there are a few small areas of atheroma in ascending aorta. *Heart*: Weight 290 gm. Diameter in situ: oblique 12.5 cm., vertical 8 cm., diaphragmatic 6.5 cm. Right ventricle is moderately dilated in region of conus; muscle is pale; wall 3 mm. thick. Left ventricle appears normal in size, muscle is firm and pale yellow; wall 17 mm. thick. Valves: circumference—tricuspid 9.8 cm., pulmonary 7 cm., mitral 8.3 cm., aortic 6.5 cm. Valves are free from verrucae and fibrous thickening. Coronary arteries appear normal. *Lungs*: Weight: left, 520 gm.; right, 500 gm. There are petechiae in pleurae, especially of lower lobes. Organs are relatively heavy, subcrepitant in lower lobes. On section the upper lobe of left lung retracts and is red; the lower lobe does not retract, is dark red. On section the upper and middle lobes of right lung are pale and exude a moderate quantity of slightly blood tinged fluid. Lower lobe is like that of the left. *Lymph nodes*: There are several slightly enlarged nodes in superior mediastinum. Retroperitoneal nodes are moderately enlarged. Their consistency is only slightly increased; on section they are dark red. There is a small mass of calcified nodes in mesentery. *Spleen*: Weight: 520 gm. There is a small accessory spleen. Fibrous adhesions on upper pole of spleen. A fairly deep fissure crosses phrenic surface of upper pole. On section: dry, brownish red; there are several slightly raised nodules about 4 mm. in diameter, paler than cut surface generally; there are smaller nodules which are believed to be Malpighian bodies. *Kidneys*: Weight: left 210 gm.; right, 180 gm. *Left*: Petechiae are seen in capsule. Capsule strips easily. Outer surface is smooth. On section cortex is pale brown and on average is 7 mm. in width. Medulla is well demarcated and averages 15 mm. There are minute hemorrhages in mucosa of pelvis. *Right*: Is similar, but is moderately congested. *Ureters*: Appear normal. *Bladder*: Appears normal. *Genitalia*: Uterus and appendages appear normal. There is a recent corpus luteum in right ovary. *Gastrointestinal Tract*: Stomach: in the mucosa are a few petechiae near cardia. Small intestine: calibre throughout this part of the gut is extremely small; there are scattered hemorrhages in mucosa. Colon appears normal. There is a small hemorrhage in mucosa of appendix. *Liver*: Weight is 2400 gm. In situ lower border is 6 cm. below CM in right mid-clavicular line, 9 cm. from ensiform. Borders are rounded. Outer surface is smooth and pale except for dilatation of capsular venules on lower border. On section surface is uniformly yellow. *Gall-bladder and ducts*: Appear normal. *Pancreas*: Appears normal. *Adrenals*: Appear normal. *Brain* is free from congestion, edema, and hemorrhages.

Microscopic Description: Heart: Left Ventricle: The most striking features are extreme edema and extreme degeneration of the muscle fibers. Cross striation is very faint, irregular, and sometimes absent. The myofibrils appear separated by edema in many of the cells. When seen longitudinally most of the fibers are frayed at their ends. Fragmentation is present, but there is so much separation of cells by

edema that the gaps are much wider than normal. The nuclei are generally pyknotic. There is no obvious hypertrophy although some of the nuclei are very large. The blood vessels are dilated but contain very few red cells. The endothelial cells are often considerably swollen. Around the vessels are spaces apparently due to edema in which a fine fibrin meshwork is visible. Fibroblasts are seen here and there and slight infiltration with mononuclear and plasma cells. Here and there the infiltration assumes the proportions of a "node." In these nodes are cells with branching protoplasm, evidently histiocytes, and other cells whose protoplasm is difficult to see but is also apparently branching and whose nucleus resembles that of an Aschoff cell.

Lungs: Right: Right lung is congested and shows alternating areas of collapse and emphysema. The alveolar walls are considerably thickened, and this is true even in the emphysematous areas. The thickening is due mainly to enormous dilatation of the capillaries and to some extent to the presence of large mononuclear cells. Some of the alveoli contain a scanty exudate of mononuclear cells with a few very large scavenger cells, a small amount of fibrin and a few red blood cells. Occasionally a giant cell is seen. Scattered over the lung substance are tiny nodes consisting of lymphocytes intermingled with a cell of the histiocyte type which resembles an endothelioid cell. These nodes are situated sometimes near arteries, sometimes in alveoli and do not appear to have any connection with the normal lymphoid tissue in the lung. The bronchi show some desquamation of the epithelium, hypertrophy of the smooth muscle and intense congestion of the vessels of the submucosa. Most of them do not contain exudate. *Left: (Lower lobe:)* The tissue stains poorly and appears more or less necrotic. All the alveoli are filled with pale, slightly granular material in which large numbers of bacteria are visible. These may be contaminants. The blood vessels contain large numbers of mononuclear cells. Fibrin is seen in many places both inside and outside the vessels. Nodules resembling those described for the right lung are present here also, except that they contain giant cells and pigment bearing cells. Many of them are seen close to large vessels. *Spleen:* The walls of the sinuses are greatly thickened and there is considerable edema of the tissue as a whole. The cells lining the sinuses are swollen, large phagocytic cells are found in several places, also giant cells with two or more large nuclei. The Malpighian bodies are edematous and germinal centers apparently absent. Some of the Malpighian bodies are necrotic. One or two nodes similar to those seen in the lung are visible although they are somewhat difficult to distinguish from normal structures in the spleen. Occasional necrotic foci are found in the pulp. *Right Kidney:* There is marked edema of the medulla together with disintegration of many of the collecting tubules. The rest of the kidney shows little or no edema. The Malpighian bodies are swollen, the loops are plump. The capillaries are open, some contain blood, others appear empty. There is moderate desquamation of the epithelial cells with swelling of those that remain. The endothelial cells are slightly swollen and stain deeply. The capsular space is moderately distended, the lining cells are slightly swollen, sometimes desquamated. Occasionally they show slight proliferation, similar to very early crescent formation. The convoluted tubules are a little dilated, the lumen contains granular material, the lining cells are somewhat granular, and sometimes disintegrating, but in many a brush border is still seen. The lesions appear most severe in the distal convoluted tubule and the loop of Henle. No casts are found in the tubules. In the fascia near one of the large arteries is a group of lymphocytes with a few histiocytes. It is uncertain whether this is a lesion of lupus erythematosus or merely a group of lymphocytes such as is often seen in the kidney. *Liver:* The liver cells show large and small vacuoles. When not vacuolated the protoplasm is extremely granular. The outlines of the cells are sometimes indistinct. Some of them are completely necrosed. The liver cells are so distorted that it is difficult to make out whether the general architecture is altered. However, except for necrotic foci, the

distortion seems to be due to the swollen liver cells which compress the sinusoids so as to render them invisible. When sinusoids are seen there is a wide Disse space containing fine fibrinous threads. The portal spaces are also edematous; they contain scattered mononuclear cells. Here and there in the liver are nodes like those seen in the lungs. They contain large and small lymphocytes, plasma cells, histiocytes and occasional eosinophiles, a fine reticular network and sometimes remains of liver cells. Somewhat similar formations are seen surrounding and enclosing groups of liver cells in the same way as fibrous tissue does in cirrhosis. This tissue is sometimes connected with portal spaces. The larger vessels, especially the veins, are dilated but they contain very few red cells. Some contain fibrin. *Lymph Nodes:* The first section shows remarkable general edema of the nodes with almost complete absence of germinal centers, considerable dilatation of the blood vessels, much less of the lymph vessels. The vessels here contain red cells. Lymphocytes are scattered evenly through the gland. Pigment bearing cells and occasional giant cells are seen. The reticulum cells are swollen. Hemorrhage is present here and there. A typical granulomatous node is seen near the center. The other node is similar but shows some indication of germinal centers. The vessels are dilated but empty; lymph sinuses are also dilated. Numerous pigment bearing cells are seen. *Adrenal:* Section shows edema, lack of cortical lipid and occasional small necroses.

Case 2. Mrs. L. L., a white housewife of 55 years, was admitted to the Woman's Medical College Hospital on June 10, 1943, for a three-stage left thoracoplasty because of bilateral chronic pulmonary tuberculosis. The first and second stages were done on June 15 and June 29, respectively, without incident.

On July 13 the third stage muscle-splitting thoracoplasty was performed. The patient's condition was good until the end of the operation, when her breathing became labored and her blood pressure dropped. She was given 500 c.c. glucose in saline and 150 c.c. blood. Through an error 150 c.c. of type 3 blood were given instead of the type 2 required. There was no chill, blood pressure remained on the same level for a short period of time. Intravenous 5 per cent glucose in saline was started as soon as error was noted, while waiting for plasma to be melted. Patient's blood pressure and pulse became barely perceptible and she went into marked shock. (Blood pressure was about 60 systolic.) She was given 500 c.c. compatible blood and continuous 5 per cent glucose in saline slowly as well as adrenal cortical extract 2 c.c. per hour. It was necessary to redress the wound twice because of hemorrhage. In the evening the blood pressure went up to 108 mm. Hg systolic and 66 mm. diastolic (at the beginning of the operation the blood pressure had been 110 mm. Hg systolic and 80 mm. diastolic). *July 14:* The patient has voided three times since operation and was catheterized three times; only small quantities (75 to 150 c.c.) of urine were obtained but the patient's condition seemed much improved. *July 15:* Yesterday's total fluid intake was 3500 c.c., the total output 850 c.c. Patient was placed on potassium citrate in hope of redissolving the acid hematin crystals which might be in the kidneys. Five hundred c.c. m/6 sodium lactate given intravenously to alkalize urine. Watermelon was given for diuresis. Late in the evening potassium citrate was replaced by NaHCO_3 because of possible toxic effect of the K-ion. Today's output practically nil—100 c.c. for 12 hours. *July 16:* Blood urea nitrogen rising, icterus index normal (see table 2). Urine loaded with crystals. Blood count is given in table 2. Temperature graph is flat, and there is great subjective improvement. No edema. Another 500 c.c. 10 per cent glucose in distilled water. *July 17:* Yesterday's output 440 c.c.; intake inadequate—1910. 250 c.c. plasma and 1000 c.c. 5 per cent glucose in saline. Blood urea nitrogen is increasing. *July 18:* Fluid output was 1230 c.c. *July 19:* Blood urea nitrogen somewhat lower. However, patient complained this morning of impairment of vision. Ophthalmoscopic examination revealed arteriosclerosis but no changes characteristic of uremia. During the afternoon

TABLE I

Date	Sed. Rate	Red Bl. Cells	Hb. Gram	Hb. %	White Blood Cells	Poly.	Lym.	Mono.	Eos.	pH	Sp. Grav.	Alb.	Sugar	Leuk.	Erythr.	Casts	Epith.	Cryst.	Blood Sugar	Blood Uren	Ict. Index
7-9-43	12	3,550,000	9.5	64	3,150	76	22	1	1	5.0	1018	Light cloud.	0	0-1	0	0	2	Many	100	12	—
7-13-43	—	2,950,000	9.0	61	3,400	72	23	4	1	—	—	—	—	—	—	—	—	—	—	—	—
7-19-43	54	2,780,000	9.0	61	3,350	80	20	0	0	—	—	—	—	—	—	—	—	—	—	—	—
7-20-43										5.0	1015	Faint trace	0	10-15	0	0	Many	Bact.	—	—	—
7-21-43																					50

Blood Culture:

7-10-43: No growth
 7-15-43: No growth
 7-19-43: No growth

Slide Agglutination

7-10-43): Negative for Typhoid H and O
 7-15-43): Paratyphoid A and B
 Proteus X19
Brucella abortus

Stool Culture:

7-15-43: *Escherichia coli*, *Staph. aureus*;
 hemolyt., coagulase negat.

Urine Culture:

7-15-43: *Staph. aureus*; hemolyt.
 coagulase positive.

the patient had several attacks of convulsions coming in short succession. The attacks witnessed by the interne were characterized by convulsions of the right arm and conjugated deviation of the eyes to the left.

Neurological consultation (Dr. Winifred B. Stewart)—essential findings: Impairment of vision, other cranial nerves normal. Biceps, patellar, triceps, Achilles reflexes all hyperactive, and perhaps right is greater than left, although this difference is not consistent. Babinski reflex is positive on right. Some weakness of right grip. All forms of sensation apparently intact. "In view of the impairment of vision and convulsions, uremia is the most likely cause of this condition. However, the fact that the convulsions are unilateral and also that the neurological findings tend to be unilateral suggest the possibility of a vascular lesion on left side."

July 20: Generalized subcutaneous edema and marked pallor are found, patient is markedly dyspneic. Râles are heard throughout the chest. The abdomen is distended but no free fluid found at examination. Blood pressure 128 mm. Hg systolic and 88 mm. diastolic. Comment of the medical consultant: "It is obvious that the patient is in very poor condition. It is probable that the fluid disturbance is on the basis of renal insufficiency. Whether the heart is contributing to the pulmonary congestion is questionable." *July 21:* Patient died.

Autopsy Findings: Gross description: General: Body is that of a well developed, well nourished white woman about 55. Lips and nails are blue. There is a thoracoplasty scar on left upper chest and a recent thoracoplasty incision in left scapular region; this wound is healed but the stitches have not been removed. Abdomen is markedly distended. There is a transverse incisional wound on dorsum of right foot. On extremities are many small circular depressed scars. *Diaphragm:* Left dome is at fifth interspace; right at third interspace. *Thoracic cavity:* The mediastinum is shifted somewhat to the left. Left lung is collapsed against the lateral and posterior wall. The voluminous right lung almost covers the mediastinum; on medial surface of upper lobe are small string-like adhesions to mediastinum. *Lungs:* Have been described in situ. Left lung was not removed because of dense universal adhesions. In upper lobe is a cavity about 4 cm. in diameter. Right lung weighs 540 gm. It is emphysematous. In the apex of upper lobe is a fibrocaseous nodule about 5 cm. in diameter; in the center is a recent cavity about 2 cm. in diameter. Also in this lobe are small healed tuberculous nodules; they are at site of adhesions described above. *Aorta:* There are small atherosclerotic nodules in the ascending aorta. *Heart:* Weight is 290 gm. In situ diameters are: oblique 12.5 cm., vertical 10 cm., diaphragmatic 5.5 cm. Right ventricle is moderately dilated; wall is 4 mm. thick. Wall of the left ventricle is 14 mm. thick. Muscle is pale brown and moist. Valves: circumferences are: tricuspid 12 cm., pulmonary 7 cm., mitral 9.5 cm., aortic 6.5 cm. Mitral valve: anterior cusp shows moderate atherosclerosis. Coronaries appear normal. *Spleen:* Weight is 125 gm. It is normal in consistency. On section surface retracts; it is pale red except for small areas of hemorrhage. *Kidneys:* Left is normal in weight and size. Capsule strips easily. On section the pale, bulging cortex is well demarcated from the medulla. Pelvis appears normal. Right kidney is large and of unusual shape. The extrarenal pelvis is enormously dilated and roughly pyramidal with apex at ureteropelvic junction. The kidney lies like a small cap over this dilated pelvis. It is remarkable that when ureter was cut the pelvis did not empty, but this phenomenon can be explained probably by the extremely small caliber of ureter at its beginning. When pelvis is opened the mucosa is found to be granular and the wall relatively thick. Calices are considerably dilated. *Bladder:* Appears normal. *Gastrointestinal tract:* Stomach is markedly distended, rugae are effaced. Transverse colon is also markedly distended. Sigmoid has a fairly long mesentery and is adherent to posterior surface of broad ligament. In the cecum there are many small acute ulcers. *Liver:* Weight is 1160 gm. In situ the lower border is 3 cm.

TABLE II

Date	Fluid Intake		Fluid Output	R. B. C.	Hb. %	W. B. C.	Stab.	Seg.	Poly.	Lymph.	Mono.	Eos.	Bas.	Turb.	pH	Spec. Grav.	Alb.	Sugar	Bile	W. B. C.	R. B. C.	Casts	Epith.	Blood Chemistry				
	CO ₂	Total Protein																						Urea N	Urea Index			
6-10; 11				3,980	70	8,100		76	16	4	2	1	1	1	7.5	1010	0	0		10-15	0	0						
7-13				3,390	64	17,800																						
7-14	3,500	850	3,390	3,390	64	17,800	18	68	86	12	2	0	0	0						No. acid hematin crystals								
7-15				2,910	61														0	8/1 mm. ³ /1 mm. ²					60			
7-16	1,910	440	3,440	3,440	69										7.5		Cloud.			5-10	0	0				58	1.45	
7-17			3,530	3,530	67										7.5	1013	Trace	0		20-40	0-1	0			52	5.8	70	9
7-18															7.0	1010	Trace	0		15-20	0-2	0	Few					
7-19			3,410	3,410	70										7.5	1007	Heavy trace	0		4-6	0	0	Many			51	20	
7-20																										66.5		
7-21															7.5	1009	Heavy trace	0		0-1	0	0	0					

Serology: Kolmer, Kline, neg.
Sputum: Positive for acid fast bacilli (6-11-43).

above costal margin in right midclavicular line and 4 cm. below ensiform. Over the lower anterior surface of right lobe the capsule is thickened and surface granular. On section lobular pattern is distinct. *Gall-bladder and ducts:* Appear normal. *Pancreas:* Appears normal. *Adrenals:* Appear normal. *Uterus and appendages:* Appear normal.

Microscopic Description: Heart: There is everywhere marked separation of the muscle fibers by edema. Cross striation is remarkably well preserved. In longitudinal sections the fibers appear stretched and are joined by elongated bands in which a few fibrils are seen surrounded by vacuoles. This may be due to dilatation. The endothelial cells of the vessels in the connective tissue are swollen; fibrin and a few mononuclear cells are seen around them. In some places there is the appearance of interstitial myocarditis (serous inflammation). In cross section the muscle fibers are irregular in size, some are very large and vacuolated. *Spleen:* The spleen is amazingly bloodless. It shows slightly dilated sinuses, lined by swollen endothelial cells. The protoplasm of these cells is scanty and in some areas there is little or no evidence of phagocytosis, but in others the cells contain irregular pink material which seems to be derived from degenerated red cells. Malpighian bodies are present, but they are small and poorly defined. The arteries and arterioles are empty, the walls are edematous; in some of them hyaline material is seen in the intima. The fibromuscular trabeculae are also edematous. *Kidney:* Under low power the most striking change is extreme edema throughout the kidney substance. Here and there are groups of distended blood vessels, surrounded by inflammatory cells. Glomeruli: Bowman's capsule is everywhere somewhat dilated. The lining cells are partly shed; those that remain are swollen and pyknotic. Sometimes the capsular space appears empty, but more often it contains a fine fibrin-like meshwork in which appear what may be shadows of cells. This material usually lies against the capsule, but in some instances fine threads connect the glomerular loops to the capsular membrane. The first convoluted tubule where it opens into the capsule is filled with similar material. A similar fine meshwork lies in all the convoluted tubules. The material appears to become condensed at the loop of Henle. At the junction of the ascending and descending loops of Henle the material becomes more condensed and granular. In a very few loops it is seen as a pinkish granular mass. Some of the collecting tubules contain the material, but most of them are empty. Occasionally clumps of shed cells are found in the tubules, but true cellular casts are not easy to find. It is to be noted that nowhere, in any of the tubules, is there anything approaching a block. In fact, the tendency is for the tubules, especially the convoluted tubules, to be dilated. A notable feature of the glomerular tufts is that no blood is visible in the majority of them. It is hard to find even one red cell in the capillary loops. Occasionally the afferent arteriole empties into a lacuna, but in only a few of these lacunae are there red cells. The capillaries on the tufts are often dilated, although empty. Many of the capillary loops contain fibrin thrombi. Many of the epithelial cells are shed, leaving the loops bare. There seems to be little or no multiplication of the cells that remain. *Convoluted tubules:* The tubules are dilated, the epithelial cells are granular and partly disintegrated. Some cells are completely degenerated; remnants of a brush border are seen in others. The convoluted tubules are separated by a narrow zone of edematous connective tissue, in which a few fibroblasts are seen. Towards the medulla the tubules are smaller, their epithelium is similarly degenerated, and they are often widely separated by edema and also by fibroblasts. The inflamed areas which catch the eye on superficial examination of the section are arranged more or less regularly (?). Close examination of such areas reveals numbers of widely distended blood vessels (the only place in the kidney where dilated vessels are found), and between the vessels a cellular exudate in which remains of kidney tubules can just be made out. The exudate consists chiefly of mononuclear cells, but in it are also a

fair number of eosinophiles and occasional polymorphonuclears. Fibroblasts are fairly numerous and more in evidence than is commonly seen in kidney lesions. This is probably because it is unusual to obtain a kidney in such an early stage of inflammatory change. The arteries are remarkably normal for a patient of 55. The afferent arterioles are edematous and show swelling of the endothelial cells. The pelvic fat is infiltrated with groups of inflammatory cells, chiefly lymphocytes. There is also an area of hemorrhage. *Liver:* The liver cells show severe degenerative changes. The liver is dotted with necrotic foci. These are often peripheral in the region of sublobular veins, sometimes central, but are not found in connection with portal spaces. Apart from the areas of necrosis the liver architecture is preserved, but the cells are sometimes shrunken and breaking up, sometimes swollen, very granular with a sponge-like protoplasm, sometimes vacuolated or distended from fatty change. Here and there a small amount of bile pigment is found in the cells. Disse's space, i.e., the space between the endothelium of the sinuses and the liver cells, is enormously distended. Fibrin threads are present in the space and in the sinuses. Blood cells are extremely scanty. In many places the Kupffer cells and the endothelial lining are destroyed. In most places Kupffer cells are rather hard to find, but when seen, are either very large or are in process of degeneration. In the necrotic areas, however, the Kupffer cells are abundant and filled with yellow pigment. They lie in a background of fibrin threads with occasional fibroblasts, and one or two mononuclear cells. The portal veins are distended but almost empty of blood, the periportal connective tissue is somewhat edematous; a few mononuclear cells are seen in it. The epithelium of the bile ducts is shed; the arterioles appear contracted.

Anatomical Diagnosis: Heart: Dilatation, edema; myocardial degeneration. *Lungs:* Thoracoplasty, pulmonary atelectasis, healed and active tuberculosis. *Kidney:* "Transfusion kidney." *Liver:* Focal necrosis. *Cause of death:* Hepatorenal syndrome due to incompatible transfusion.

DISCUSSION

Both of these cases demonstrated severe generalized visceral edema with changes in the parenchyma of several vital organs (especially the heart, kidney and liver). Both cases showed marked alteration of the cells of the reticulo-endothelial system. The immediate cause of death was failure of the parenchymal organs. Both cases showed transitory cerebral symptoms before death.

It is of interest that the post-transfusion survival period in case 1 was a matter of hours; whereas, in case 2, it was longer than one week. Case 1 received only 250 c.c. of blood presumably compatible, although nothing is known concerning the titer of the serum used for testing.⁸ Case 1 received 150 c.c. of incompatible blood (through an error in labeling). In both instances fatal reactions followed relatively small transfusions. This is at variance with the tendency to determine prognosis on the basis of the amount of reaction-producing blood transfused.¹¹

Preëxisting reticulo-endothelial disease may have been a determining factor.

The speed of administration of blood in case 1 (something less than 3 c.c. per minute) does not appear to be an important consideration. There was no evidence of pulmonary congestion or edema at the onset of the reaction.

Moreover, prior to transfusion, there was no clinical evidence indicating a diminution of cardiac reserve incapable of supporting a greater load.

The cerebral symptoms might be attributed to renal failure in case 2, but this is impossible for case 1. However, the symptoms resemble the observations of Lehane⁷ and of Robinson,⁸ who saw transient blindness and temporary mental disorder appear a short time after blood transfusions. Lehane⁷ indicates five possibilities for the explanation of this phenomenon but finds all of them wanting. The writers feel that edema of the central nervous system is the most likely cause, with cerebral ischemia due to or increased by hypotension as an alternate possibility.

The major symptoms at time of death were those of oliguria, hyposthenuria (especially in case 2), retention of urea, and evidence of icterus. Originally the picture of kidney damage after transfusion was ascribed to the blocking of the renal tubules by acid hematin precipitates.⁹ However, there is no evidence of a block of the tubules in either case, and the purely mechanical explanation of anuria does not hold true. Baker and Dodds¹⁰ interpretation has found many opponents in recent years.^{10, 11, 3, 4}

The icterus, visible at autopsy in case 1 and well established by laboratory tests in both cases, can be explained on the basis of hemolysis or hepatocellular disturbance. Although in case 1 icterus appeared overnight, in case 2 it developed late (long after the hemolytic process could account for it). On the other hand the marked and widespread damage of the liver cells in both cases suggests an hepatocellular jaundice.

Furthermore, we are able to trace the development of the edema in case 2. The figures for fluid intake and output show that there has been hidden tissue edema as early as July 16, when the icterus index was still low. We may conclude, therefore, that—at least in the case of the liver—signs of tissue damage have *followed* the appearance of generalized edema. Since renal and hepatic symptoms coexist, from a clinical standpoint the term post-transfusion hepatorenal syndrome is permissible here.

Tissue parenchymal damage in its relation to edema has been studied by Eppinger and his associates,¹² who gave a new meaning to the old term of "serous inflammation." It is most common in the liver, but pathogenically similar lesions in the kidneys have been described.^{2, 6, 13} Endogenous "capillarotoxic protein split products" have been held responsible for producing them. Such a mechanism seems to apply in the production of the visceral lesions observed at autopsy in these cases. The parenchymal lesions might well be considered the sequelae of tissue edema resulting in variable degrees of tissue anoxia with consequent capillary damage.

CONCLUSIONS

The cases presented in this report show not only the renal pathologic lesions seen in post blood transfusion reactions and changes in the liver, but also generalized and widespread visceral and tissue edema. The findings

in case 1 indicate that this edema is not the result of renal failure, since sufficient time could not have elapsed for this development. Case 2 appears to fall into the same category, in view of the evidence of water imbalance causing hidden tissue edema noted long before failure of the kidney and liver parenchyma became clinically apparent. It is possible, if not probable, that the autopsy findings in these cases were conditioned by the preëxisting reticuloendothelial disease. Should this be the case, certain considerations become of paramount importance: (1) The symptoms are usually characteristic of renal disturbance, but clinical and laboratory evidence may reveal liver involvement. In this instance the term hepatorenal syndrome is permissible. However, the arrival at this conclusion should suggest that visceral (parenchymal) involvement may not be confined to the kidneys and the liver. It may involve other organs: heart, brain, and lungs. (2) The occurrence of widespread interstitial edema makes one wonder whether the usually recommended therapy in cases of hemolysis due to incompatible blood transfusion should be employed in cases such as those here reported. The forcing of fluids, especially where oliguria or anuria exists, would tend to increase tissue edema. It would seem to these writers that technics designed to prevent and control tissue edema would be desirable. Thus, plasma and, perhaps, hypertonic solutions, may be employed. The use of mercurial diuretics should be considered to mobilize extrarenal water. Substances capable of improving capillary function, such as ascorbic acid, adrenal cortex hormone, and calcium, may be employed with benefit.

SUMMARY

1. Two cases of fatal transfusion reactions with autopsy findings are described.
2. Although death occurred in a matter of hours in one case and after one week in the other, the pathologic findings were similar. Widespread visceral edema was seen in both cases.
3. Transfusion reactions and death occurred after 150 c.c. of incompatible blood were administered in one case and 250 c.c. of blood in the other.
4. The patho-physiologic aspects are discussed. The possible effect of prior reticuloendothelial disease as a conditioning factor in the production of widespread visceral involvement in transfusion reactions is mentioned.
5. Changes in therapy are considered.

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THE BEHAVIORAL RESPONSE OF PATIENTS SEIZED WITH AN ACUTE MYOCARDIAL INFARCTION *

By STUART W. McLEOD, M.D., *Rochester, New York*

THE clinical features associated with an acute episode of a coronary occlusion with myocardial infarction are so well known to the medical profession today that the diagnosis of this condition is usually made with ease on the basis of the history and physical examination. This has been due to the pioneering work of Herrick,^{1, 2, 3} Dock,⁴ Wearn,⁵ and Levine⁶ as well as others who were among the first to point out the essential symptomatology and physical findings upon which the diagnosis rests.

The purpose of this paper is to present an additional feature of the disease which may be of value in some instances in making a clinical diagnosis of this condition when it otherwise might be a matter of doubt or hesitation. The manifestation about which I wish to call attention is the instinctive response of the individual seized with a coronary occlusion to his pain. It is my belief that this response is one of effort, and that in this respect it differs from that which occurs in the symptom complex known as angina pectoris.

In angina pectoris the patient usually complains of an oppressive substernal or epigastric sensation which may radiate to the arms, neck, or back. This pain comes on after effort or after eating and is relieved by rest. What is most significant is that the afflicted person automatically stops all effort as soon as he is seized with his pain. Neither friend nor physician must tell him to rest. He will do it without being told. This behavioral reaction of the individual suffering from angina pectoris to his pain has been known for years. For the purposes of this paper, this will be considered the definition of angina pectoris.

The character of the pain associated with angina pectoris and with a coronary occlusion is usually the same. The features that commonly distinguish the two conditions are these: In angina the pain is of short duration; frequently it is less intense but not always so; and finally systemic effects are absent or transient.

The description of the acute episode of a coronary occlusion as given in three textbooks^{7, 8, 9} consulted emphasizes the picture of collapse, which is frequently present early in this condition. The inference which is easily drawn by the reader from these descriptions is that the patient probably reacts to the pain of an acute coronary occlusion as he would to an anginal attack. Namely, he desires to rest. However, it must be remembered that when the patient is first seen by a physician, several hours may have

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elapsed from the time of onset of symptoms. By this time the patient usually is in the state of collapse described. However, when the patient's symptoms are considered in relation to time, the majority of patients seized with an occlusion will show varying periods of activity immediately following the onset of their pain. This period of activity may then be followed by the desire or necessity to rest. Therefore, the state in which the patient is first seen does not necessarily represent the state he may have been in immediately following the onset of his symptoms.

The conclusions presented in this paper are drawn from observations made on 28 successive patients suffering from acute myocardial infarctions. All of these patients were observed personally. These attacks were initial ones in so far as it could be determined from all available evidence. This point is emphasized. Frequently patients, who have suffered from one occlusion, suffer further episodes of pain. These episodes may appear to be further occlusions. However, it is often difficult to establish by the usual clinical and laboratory means exactly what has happened to the myocardium. For this reason episodes of a coronary type of pain occurring in those individuals known to have had a previous occlusion were not included. Therefore, the conclusions presented here do not necessarily apply to this class of patients.

In this group, 22 patients were male and six female. Sixteen survived and 12 died. Of the 12 who died, 10 came to autopsy, and the diagnosis was confirmed post mortem. The usual clinical and electrocardiographic criteria were followed in making the diagnosis, i.e. the presence of a characteristic pain and a clinical course accompanied by some or all of the following: Fever, elevation in white blood count, elevation in sedimentation rate, drop in blood pressure, presence of a gallop rhythm, or presence of a friction rub. Of the 16 patients who survived, 13 had classical changes in serial electrocardiograms to confirm without doubt the clinical diagnosis. Three cases were included in which there were significant changes demonstrated in serial electrocardiograms, but not classical changes. However, other features of the illness in these three individuals made the diagnosis appear so definite that all observers who saw the patients were in agreement.

The procedure followed in this investigation was to question all patients in detail as to symptoms suggestive of angina pectoris prior to the onset of their present illness. In addition, they were questioned as to the nature of their acute pain, its radiation, and its duration. They were also encouraged to recall exactly what they were doing when the pain first occurred, and what they immediately did thereafter. The usual routine history and physical examination were done as well.

It was of interest to note how vividly most of the patients could recall with accuracy just what they did. There were a few patients who at first did not understand what was wanted of them. These individuals had not considered their activity following the onset of their pain as anything that would be of interest to the examiner. If a leading question had to be asked,

it was stated in a manner such as this: "Did you remain sitting in your chair?," or if the patient was in bed at the time of the attack: "Did you remain in bed?" It was felt that if suggestion had to play a part in eliciting information, it would be better to ask the question opposite to the anticipated answer. A few patients were so acutely ill at the time of admission that detailed questioning was deferred until later. This was usually true of those patients admitted with acute pulmonary edema, which had been precipitated by a coronary occlusion.

Of the 28 patients interviewed, 18 stated that they immediately walked about with the definite feeling that walking or movement might provide them with relief. An additional four patients gave a history of walking, but they had no conception of why they did it. As far as these individuals were concerned, they just walked. Another five patients felt that their activity was motivated by the necessity to vomit, urinate, or defecate, and that the walking was necessary to get to the bathroom where these things could be most easily done. Only one patient showed no activity of significance. The duration of the activity was as follows:

Eleven patients showed a period of activity from five to 15 minutes; five patients showed a period of activity from 15 minutes to one hour; four patients showed a period of activity from one to two hours; seven patients showed a period of activity from two to 15 hours.

Several patients experienced premonitory attacks of pain. On reviewing the exact nature of the pain, its duration, and its severity, it was difficult to distinguish the premonitory episode from the one which was considered to bring about the final occlusion of the vessel. However, some of the patients who had premonitory pains described them as less intense and shorter in duration than the final attack of pain. The significant feature in regard to the premonitory type of pain was that the patient responded by walking if he had been at rest or usually continued his work if the attack came on while he was working.

As far as could be determined from the patients in this series, activity was an immediate response and was not engaged in after a trial period of rest had failed to relieve the pain. This point was best exemplified by those patients who previously suffered from angina pectoris. These individuals stated that they had no thought of resting as they did with their anginal attacks but immediately began some form of effort.

Five cases will be presented, which illustrate the variety of responses obtained in the group as a whole.

CASE REPORTS

Case 1. R. L., a 75 year old white, married male, was in fair health until the morning of April 4, 1947, when he was awakened from a sound sleep by a severe pressing substernal pain. He immediately sat up in bed and rubbed his precordium violently. In a few moments, he got out of bed and walked to the bathroom where he attempted to have a bowel movement and vomit. He then walked back to his bed-

room, called his wife, and went to bed. He progressed rapidly into a state of peripheral vascular collapse and was brought into the hospital about two hours later in very poor condition. However, he was able to give a good account of his symptoms. His past history was essentially negative, except that during the past six months he had suffered from a vague epigastric distress, which conceivably may have been an anginal type of pain. It was not possible to go into detail on this point because of the patient's condition. The physical examination at the time of admission revealed a thin, acutely ill, white, elderly male, lying quietly in bed breathing with a mild Cheyne-Stokes respiratory rhythm. The temperature was 101°, pulse 140, respirations 20, and blood pressure 55/0. The skin was pale, cool, and moist with moderate cyanosis of the lips and extremities. The lungs showed fine moist râles at both bases. The heart was not enlarged to percussion, and M₁ was absent. At times a gallop rhythm was audible over the precordium. The only laboratory examination done was an electrocardiogram, which showed elevation of ST₁ and ST₄. The QRS complexes were slurred and notched with an intraventricular conduction defect. The patient died 16 hours after admission. At autopsy a massive anterior myocardial infarction was discovered with atherosclerosis of the left coronary artery with thrombus formation present in the first third of the left coronary artery.

Case 2. S. W., a 78 year old widow, had been in good health until the morning of Sunday, April 13, 1947, when she was seized with a severe pressing pain in the back between both scapulae. She was riding on a bus at the time on her way to church. She continued on her way, and the pain abated. Twenty minutes later while sitting in the church, she was seized with a severe constricting pain beneath the sternum radiating through to the back. She thought that she might feel better if she could get up and walk. She left the service and walked out to the vestibule where she paced about for ten minutes but had no relief from her distress. A taxi was summoned, which took her home, and from there she was sent into the hospital. Her past history was negative, except for possible hypertension. She had been in extremely good health all her life. Physical examination at the time of admission showed a well developed, elderly, white female lying quietly in bed complaining of severe precordial distress. The temperature was 99°, pulse 100, respirations 20, and blood pressure 150/80. The skin was warm and dry without cyanosis. The lungs were clear to percussion with rhonchi audible throughout both lung fields and moist râles at both bases. The heart borders could not be percussed accurately. The heart sounds were of poor quality and easily obscured by the breath sounds.

No electrocardiographic or laboratory studies were made before death. The patient gradually went into peripheral shock and died five hours after admission. Autopsy showed occlusion of the left coronary artery with rupture of the intraventricular septum.

Case 3. F. P., a 59 year old mechanical engineer, was in good health until 8:30 on the morning of March 30, 1947, when he was seized with a sense of fullness in the epigastrium. It felt as though there was some gas in the stomach which could not be brought up by belching. This fullness was soon merged with a squeezing and pressing sensation in the precordium, which radiated down both arms. Immediately after the onset of pain, he got up and walked up and down the living room for about three hours without once sitting down. He felt no better after this time and a physician was summoned who came and found him still pacing up and down the floor. A diagnosis of a coronary occlusion was immediately made and the patient sent into the hospital. His past history revealed that he had been feeling tired for about one year, and that he had occasional episodes of indigestion and constipation. However, these bore no relationship to effort or to meals, and no clear conception could be gained as to their cause. He had been in the hospital six weeks prior to the present admission at which time sigmoidoscopy, barium enema, and an electrocardiogram were all normal.

Physical examination showed a well developed and well nourished, slightly obese, white male with a florid, healthy appearance. His temperature was 98.6°, pulse 84, respirations 17, and blood pressure 130/80. The skin was warm, dry, and without cyanosis. The lungs were clear to percussion and auscultation. The heart was enlarged slightly to the left. The sounds were of fair quality.

The laboratory findings on admission showed a white blood count of 7,600 and a sedimentation rate of 10 mm./hour.

An electrocardiogram taken on March 31, 1947, showed all ST segments to be isoelectric. T₁ was isoelectric and T₂ was deeply inverted and cove shaped. The electrocardiogram taken six weeks previously showed T-waves upright in all leads. Another electrocardiogram taken on April 11, 1947, showed T₁ and T₂ inverted with T₂ more deeply negative. A final electrocardiogram taken on May 2, 1947, showed T₁ upright and T₂ less negative.

While in the hospital, the patient ran a low grade fever between 100° and 101° for the first five days, and then it returned to normal. His sedimentation rate became elevated for a time, and he displayed a gallop rhythm for a few days shortly after admission. Except for a few recurrent episodes of precordial distress coming on after meals, he did well and was discharged to his home on the thirty-eighth hospital day.

Case 4. J. C., a 55 year old common laborer, had been in good health until the first week of July, 1947, when he began to notice the frequent occurrence of substernal pressure following exercise, which was relieved by rest. Whenever this pain occurred, he instinctively stopped all effort. About three o'clock on the afternoon of August 3, 1947, while sitting on a park bench, he was seized with a sudden and severe sense of substernal oppression and squeezing. The pain radiated down his left arm. He immediately arose from the bench and walked about for a few minutes. Then he walked over to a nearby lunchroom and bought a bottle of ginger ale with the idea that it might help to bring up gas, which in turn might relieve his discomfort. This did not happen, however, so he went back to the park and sat down on the bench for a few minutes and then again got up and walked about until the pain gradually subsided in intensity. He then walked a mile to the emergency department of this hospital where he was immediately put to bed and given morphine to relieve his residual discomfort. His past history revealed that he had a hypertension of over 200 for several years, and that he had been treated for syphilis.

Physical examination showed a well developed, ruddy faced, white male, who did not appear particularly ill. His temperature was 100.6°, respirations 18, pulse 80, and blood pressure 174/106. The heart was not enlarged, and the sounds were of fair quality without murmurs.

The laboratory findings showed a white count of 9,600 on admission and a sedimentation rate of 37 mm./hour. An electrocardiogram taken on August 4, 1947, showed slight slurring of QRS in all leads with T₁ inverted, T₂ isoelectric. There was an absent R_s; ST₁ was slightly elevated with a deeply negative T₁. Another electrocardiogram taken on August 9, 1947, showed ST₁ slightly elevated with coving of T₁. There was moderate elevation of ST₁ with a diphasic T₁. A final electrocardiogram taken on August 25, 1947, showed T₁ deeply inverted with ST₁ isoelectric with a T₁ so deeply inverted that the apex could not be recorded on the paper.

While the patient was in the hospital, he had a low grade fever for five days. He had a definite gallop rhythm during his first week in the hospital. He was discharged improved on the thirty-fourth hospital day.

Case 5. W. U., A 64 year old retired business man, was seized with a pressing epigastric non-radiating pain about 11 o'clock on the evening of August 3, 1947. He was sitting in a chair reading at the time. A few moments after the onset of the pain, he arose from his chair and walked to the kitchen, where he took a shot of whiskey with the hope that it might relieve his discomfort. However, it grew worse, and he

walked upstairs to his bedroom. After a few minutes in bed, he walked to the bathroom and vomited. He still was not relieved from his pain, so he walked up and down his upstairs hallway for about one-half hour, hoping that the pain would subside. Finally his wife suggested that he lie down, and a physician was called who made the diagnosis of a coronary occlusion and gave him morphine for relief. He was sent into the hospital by ambulance the following morning. His past history was significant in that he had been a known hypertensive for 15 years, and that five years prior to this admission he developed typical angina pectoris. His anginal episodes had been characterized by the presence of a precordial pressing sensation with radiation of pain down the left arm. The episodes came on after effort and ceased with rest. The angina lasted for about one year and gradually disappeared so that the patient was completely free of angina on ordinary effort for about three and one-half years prior to this episode. The pain associated with his occlusion differed in location and nature from that which he experienced with his angina.

The physical examination at the time of admission was not remarkable. The patient did not appear acutely ill. The temperature was 99°, the pulse 110, the blood pressure 150/120. The lungs were clear. The heart was enlarged to the left. The first heart sound was of fair quality. The rhythm was regular, with the exception of occasional premature contractions.

The laboratory findings showed a white count of 19,100 on admission, and the sedimentation rate was 15 mm./hour. An electrocardiogram taken on August 4, 1947 showed slight elevation of ST₁ with inversion of T₁. R_s was absent. ST₄ was elevated, and T₄ was inverted. An electrocardiogram taken on September 10, 1947, showed a characteristic "healing" stage of an anterior myocardial infarction.

While the patient was in the hospital, his temperature rose to 102° and remained there for six days and returned to normal gradually during the following two days. The sedimentation rate became elevated to 40 mm./hour. He also presented a gallop rhythm for several days following admission. About one month after admission while appearing to get along well in every way, he developed acute pulmonary edema and was digitalized. He had no further difficulties and was discharged from the hospital seven weeks after admission. He died with acute pulmonary edema while at home one month later. An autopsy was not obtained.

The activity shown by the following patient was so minimal that it was impossible to interpret it as anything other than the type of response anticipated in angina pectoris.

Case 6. S. M., a 55 year old white plumber, was in fair health until August, 1947, when he noted the occasional occurrence of a full feeling in the epigastrium, which he thought was indigestion. This fullness came on after effort and was relieved by rest. At four o'clock on the morning of September 8, 1947, he was awakened from a sound sleep by the same type of pain, which he had had previously on effort. This time the pain was more severe and gradually radiated over the precordial area and down both arms. Soon after its occurrence, he sat up in bed and rocked backwards and forwards slightly. He did not leave his bed nor did he engage in any more activity other than that described. He was seen by his physician about four hours later. He was given nitroglycerine sublingually without relief. He was then given morphine and sent into the hospital. He had no vomiting, dyspnea, cyanosis, or diaphoresis. His past history included a subtotal thyroidectomy at the age of 15, a cholecystectomy at the age of 48, and a radical right mastectomy for carcinoma of the breast at the age of 50.

The physical examination showed a well developed, muscular, middle-aged, white male, who appeared in mild distress. His temperature was 98°, pulse 100, respirations 17, and blood pressure 180/130. The lungs were clear to percussion and auscultation. The heart was enlarged to the left, and an apical grade II systolic murmur was audible. The heart sounds were of fair quality.

The laboratory findings on admission showed a white count of 16,700 and a sedimentation rate of 33 mm./hour. An electrocardiogram taken on September 9, 1947, showed gross elevation of ST₁ and ST₂ with T₂ and T₃ inverted. The QRS complexes were grossly slurred and notched. R₄ was absent.

While the patient was in the hospital, he developed a temperature of 104° the day following admission, and it ranged between 102° and 104° for five days, when it gradually returned to a normal level during the next three days. A pericardial friction rub was audible for about 12 hours on the second hospital day. He then developed a definite gallop rhythm, which was present for about five days. He remained in the hospital for three weeks and was sent home to continue bed rest. He died two days later. No autopsy was done.

In the case that follows the acute episode of pain was mild. When I saw this patient I was doubtful as to the significance of the incident when I considered only the duration of the pain and its severity. The physical findings were meager. My first impression was to refer him for further ambulatory study. However, consideration of the behavioral response to the pain and especially the consideration of the fact that it differed from the previous response to a similar pain made me conclude that the man probably had a coronary occlusion, and I admitted him for further study. Therefore in this particular patient I felt that the knowledge of the behavioral response was the additional piece of evidence that allowed me to treat the man as he should have been treated. Otherwise, I am sure that I would have allowed him to remain ambulatory until further developments forced the true state of affairs to my attention.

Case 7. W. W., a 64 year old unemployed factory worker, had been in fair health until the middle of July, 1947, when he noted the frequent onset of a heavy pressing pain in the substernal and epigastric area after eating and after exercise. This pain would disappear after rest. On the evening of August 22, 1947, he felt the same discomfort, but rather than resting he felt like walking about to relieve his pain. He walked about for two hours until the pain gradually subsided. He came into the emergency department of this hospital the following morning to find out what could be done for him. He felt that the pain had not been any more severe than on previous occasions, but for some reason he was definitely more concerned about it than he had been about his anginal attacks. His only other complaint was that he had been slightly more dyspneic following the attack of pain on the previous night than he had been previously. His past history was otherwise non-contributory.

Physical examination showed a thin, lanky white male who did not appear acutely or chronically ill. His temperature was 98.6°, pulse 104, respirations 20 and blood pressure 130/80. The lungs were clear to percussion, but there were a few fine râles at both bases. The heart was not enlarged, and the sounds were of good quality without murmurs.

The laboratory studies on admission revealed a white blood count of 37,900, and a sedimentation rate of 34 mm./hour. An electrocardiogram taken the day of admission showed slight sagging of ST₁ and ST₂ with moderate sagging of ST₃. T was upright in all leads. There was an early intraventricular conduction defect in all leads. Another electrocardiogram taken on August 26, 1947, showed all QRS complexes to be of lower voltage when compared with the previous tracing. T₁ was isoelectric and T₂ was of low voltage. A final electrocardiogram taken on September 3, 1947, showed all ST segments to be isoelectric and T₁ and T₄ inverted with T₂ isoelectric.

While the patient was in the hospital, he ran a temperature varying between 100° and 100.8° for three days. His sedimentation rate remained elevated for three weeks and gradually returned to normal. Toward the end of the fourth week he experienced some further precordial pain on effort. He was discharged improved after five weeks in the hospital.

DISCUSSION

In summary, I believe that a distinction can be made between the pain of angina pectoris and that associated with a coronary occlusion on the basis of the inherent behavioral response of the individual to his pain. The patient with angina pectoris characteristically has his pain on effort, and the instinctive response to this pain is cessation of all effort and motion. On the other hand, the patient seized with a coronary occlusion is frequently at rest although he may be at work, and his instinctive response to this pain is effort lasting from five minutes to several hours. Effort in this series of patients was manifested as walking.

The frequency of this response can probably be visualized best by a consideration of the normal distribution curve. This curve applies to the frequency of occurrence of most biological phenomena. There will undoubtedly be occasional cases such as the one described here that do not present this behavioral response, as there are undoubtedly cases of coronary occlusion that do not have pain. However, the greatest number of patients should show a period of activity immediately following their acute episode of pain ranging from 10 minutes to four hours. Activity less than or more than this should occur with decreasing frequency.

An understanding of the usual behavioral response of a patient with a coronary occlusion is also helpful in distinguishing a genuine occlusion from a simulated occlusion. Those patients whose symptoms are motivated either by obvious malingering or on a more subtle neurotic basis usually convey the idea to the examiner that their pain causes complete and immediate cessation of all activity. The neurotic or malingerer will not show activity following the onset of his pain.

It is my belief that all patients who appear to have a definite coronary type of pain and respond to their pain with some evidence of effort should be considered as potential coronary occlusions. If this distinction is followed, there will be some cases admitted for study in which the diagnosis will be difficult to establish electrocardiographically. This has occurred in two patients during the period of this study. The possibilities that have to be considered are that these two individuals either did not have an occlusion, or if they did have one, the myocardial damage was so minimal that no changes of significance could be discovered. Finally, they may not have had heart disease, and their symptoms may have been due to some other undiscovered cause. Intensive follow-up studies on this type of patient should be helpful in further evaluating the reliability of this factor.

SUMMARY

Twenty-eight cases of coronary occlusion with myocardial infarction are presented, of which 27 showed an immediate response to their pain of effort lasting from five minutes to 15 hours. The general thesis is advanced that

an additional distinction can be made between the pain of angina pectoris and that associated with a coronary occlusion on the basis of the behavioral response of the patient to his pain.

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AN HISTORICAL REVIEW OF THE PHYSICAL EXAMINATION OF THE CHEST*

By F. M. POTTENGER, M.D., F.A.C.P., *Monrovia, California*

THERE is no part of medicine that offers so great a challenge to the medical mind as diagnosis. Early diagnosis detects disease when the least harm has been done to the patient and makes treatment more simple and cure more probable. Then too, if the disease is infectious, it permits early application of public health measures for the protection of others.

Any method of examination which adds to the earliness or the certainty of diagnosis is a valuable contribution to the welfare of man.

For a long time it was thought that disease was a general disorder involving the whole organism. However, in 1761 Morgagni¹ published his book on pathological anatomy, and Auenbrugger² devised percussion for the examination of the heart and lungs. It was thus shown both pathologically and clinically that some illnesses had their seat in organs.

It is nearly two centuries since the physical examination of organs within the chest was made possible by Auenbrugger through percussion, and a century and a quarter since their examination by auscultation was made possible by Laennec and the stethoscope.

There is no record of percussion having been used in the examination of the organs of the chest prior to 1754, when Leopold Auenbrugger of Vienna struck the normal chest of a patient with the tips of his fingers and noted a resonant sound. However, Skoda states that the abdomen had been previously percussed to determine the presence of gas in the bowel. Auenbrugger found that a stroke over the heart gave a dull sound and over a normal lung a resonant sound. However, he also noted that when the lungs were diseased a different sound was elicited. He found, on post mortem, that those areas of the lungs over which he had obtained a dull note on percussion contained less air than normal and that those which showed hyperresonance contained more air than normal. After seven years of percussion and noting sounds and comparing clinical and postmortem findings, Auenbrugger in 1761 published *Inventum Novum*, a small book of 95 pages which contained the results of his clinical observations, describing resonant, dull and tympanic notes—the conditions responsible for all of which he had proved post mortem.

The following quotation from *Inventum Novum* is taken from a translation published in Castiglioni's History of Medicine:³

"I. The thorax of a healthy person sounds, when struck.

"II. The sound thus elicited from the healthy chest resembles the muffled sound of a drum covered with a thick woolen cloth or other envelope. . . .

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"XII. If a sonorous part of the chest struck with the same intensity yields a sound deeper than natural, that part is diseased where the note is deeper.

"XIII. If a sonorous part of the chest struck with the same intensity yields a sound duller than natural, disease exists in that part. . . . I have opened the bodies of many dead from this disease (consumption) and I have always found the lungs firmly bound to the pleura, and the lobes on that side where the obscure sound has existed callous, indurated, and more or less purulent."

Auenbrugger is supposed to have obtained the idea of percussion from seeing his father, who was an innkeeper, tap on wine barrels to estimate their contents. However, the fact that he lived in Vienna at the time of Gluck and Haydn and was himself a devotee of music might also have had much to do with it. He not only was a distinguished physician but also entered into the cultural life of Vienna. He was a Styrian, born in Gratz. In 1784 the Emperor gave him a patent of nobility. Auenbrugger wrote an opera, *The Chimney Sweep*, which would indicate that he had a high appreciation of musical tones.

Van Swieten was head of Viennese medicine and was greatly admired by Auenbrugger. He and his successors, de Haen and Stoll, taught the necessity of studying the patient. DeHaen introduced the thermometer into Viennese medical circles. However, not one of these clinicians saw that Auenbrugger had opened new vistas in medicine. In their writings on diseases of the chest not one of them recommended percussion, but Stoll mentioned it in his Aphorisms. This caused Auenbrugger great disappointment, but he said he expected such treatment of his discovery and did not let it dissuade him from continuing his observations.

Although percussion had within it the possibility of furnishing a better understanding of chest diseases, physicians were slow to adopt it, and Auenbrugger died without its being accepted.

About 50 years later Corvisart, finding little progress in France, turned to Viennese medicine, which was in the ascendancy at the time. He learned of percussion through his translation of Stoll's Aphorisms. Percussion had not come to his attention in Paris. In fact, it was all but forgotten. But Corvisart on learning of it was immediately impressed with its possibilities. He used it daily in practice and did everything in his power to induce others to use it. In 1808 Corvisart⁵ brought out an elaborate translation of *Inventum Novum*, expanding it from its original modest 95 pages to 440 pages.

On hearing that Corvisart diagnosed diseases of the chest by examining that part of the body direct, Napoleon, who was ill, said: "Send him to me." Corvisart came and tapped Napoleon's chest with his fingers and made a diagnosis. This so impressed Napoleon that he appointed him his personal physician. It was from this vantage point that he was able to revive percussion and establish it for all time, but not without great opposition on the part of his confreres.

As professor of practical medicine in the College of France, he taught that diagnosis depends on accurate observation.

Corvisart not only revived the almost forgotten percussion but stimulated his distinguished pupil, Laennec, to observe and examine. Laennec was a student of acoustics and also a musician (player of the flute), therefore it was not unnatural that his attention should be turned to percussion and auscultation. Laennec not only felt the pulse and percussed the heart, but he listened to the heart sounds with his ear to the chest. This was often disagreeable—sometimes to the physician on account of the lack of cleanliness; sometimes to the patient on account of modesty. It is said that 15 days before he discovered the stethoscope he read a paper on immediate auscultation before the Societe de L'Ecole, which not only shows his great interest in auscultation before he discovered the stethoscope but also indicates the suddenness of his discovery. This was in February 1815. It is said to have been the first paper recorded on *immediate* auscultation, and yet *mediate* auscultation was just about to be born.

The story of the discovery of *mediate* auscultation is the following. Laennec had a very obese woman patient whose heart sounds he could not hear clearly. The patient was not only obese but modest and he could not bring his ear in contact with the area of the heart sounds. He saw some boys playing with timbers lying in the courtyard of the Louvre. One of the youngsters tapped on the end of a long beam and another put his ear to the other end and could hear the transmitted sound. This gave Laennec an idea. On arriving in the presence of his patient he made a roll of paper, put one end over the site of the cardiac impulse and with his ear to the other end heard the sounds with unusual distinctness. He then listened to the lungs and heard the respiratory sounds with clearness and satisfaction. In this manner the stethoscope was discovered and Laennec was able to report the first description of the sounds heard on respiration.

For four years Laennec worked, observing patients and, like Auenbrugger, when possible compared his findings with postmortem results. In 1819 he published his observations on the use of the stethoscope in the study of diseases of the heart and lungs. In this he described the respiratory sounds as he heard them in normal chests and in the various diseases of the lungs.

Laennec's book *De L'Auscultation Médiate* (Paris 1819), like *Inventum Novum* of Auenbrugger, was given a poor reception. Many saw in the stethoscope no advantages over previous methods of examination and feared that mechanical instruments would ruin clinical observation. What would they think of today's armamentarium?

Those who refused to see value in it were those especially who had not seen its demonstration, but those who witnessed Laennec's demonstrations were convinced. The numbers of his pupils were many, and the French school prospered. Skoda of Vienna and Piorry of Paris both adopted and enthusiastically demonstrated percussion and auscultation. Piorry^{7,8} was

the first to use the pleximeter. He also taught the value of the resistance felt by the percussing fingers, although Corvisart had the honor of being the first to note this phenomenon.

Physical diagnosis based on percussion and auscultation was gradually established. It was fortunate to have as its sponsors, Auenbrugger, Laennec, Corvisart, Piorry and Skoda.⁹ In two of these the spark of originality had lighted the way to a newer clinical conception, and the others were far-sighted enough to recognize the value of these discoveries to medicine and the world.

Medicine had made great advances in the 50 years following the discovery of percussion and should have been better prepared to receive the work of Laennec, yet it was received only half-heartedly. But it was saved by the enthusiasm of a few great teachers who came in contact with Laennec and others who followed him.

Many physicians from different parts of the world came to Paris to study with Corvisart and Laennec. This made Laennec's work too arduous for his frail body. He was suffering from tuberculosis and was compelled for a time to give up his teaching and to repair to his old home in Brittany. His enthusiasm, however, compelled him to return to his work sooner than he should have done. He observed, he taught, he wrote; and, in 1826, just after finishing a second book¹⁰ Laennec fell seriously ill and soon thereafter died.

Laennec stated: "Immediate auscultation, however, should not cause us to forget the method of Auenbrugger; on the contrary, it confers on it an importance altogether new, and extends its use to many diseases in which percussion alone affords no indication." He was exceedingly optimistic about the readiness with which physicians could master auscultation. He stated: "It is, however, sufficient to have observed a disease two or three times to know how to recognize it with certainty."

Laennec stated that immediate auscultation was tried by Hippocrates but there was no evidence that from the time of the Father of Medicine to his time anyone had repeated the experiment.

Laennec paid little attention to expiration. He was particularly engrossed with the idea that he was able to hear the air pass down through the bronchi and into the alveoli. Starting with the trachea, he spoke of tracheal breathing; he followed, in his mind, the air through the bronchi and called that *bronchial breathing*. Then he assumed that the air cells were opening and called that *vesicular breathing*. Combinations of the latter he called *broncho-vesicular*.

He assumed that the murmur which he heard originated in the pulmonary tissues and bronchi immediately under the stethoscope. This is partly true. The pulmonary tissues do have a part but not the only part in the production of the respiratory murmur, and also a part but not the only part in its transmission to the ear, as may be inferred from the murmur produced and transmitted over the abdominal muscles in abdominal breathing.

He described the finding of *bronchial breathing*, normally, over the large bronchi near their bifurcation; and *vesicular*, in the axilla near the surface of the lungs at the end of the bronchi, particularly, where they passed into air cells. Bronchial breathing heard elsewhere he considered pathological; likewise the failure to find vesicular breathing where it was expected to be. He reasoned that when the air cells are filled with exudative material the only sound heard must be that of the bronchi, hence pneumonia and tuberculous consolidation cause bronchial breathing. He noted the increased intensity of the spoken voice, *bronchophony* in case of infiltration of the lung; and the transmission of distinct syllables, *pectoriloquy*, in case of cavity. It must be remembered that many of his patients suffered from far advanced tuberculosis, with cavitation. The recognition of early lesions is a recent accomplishment.

Laennec also gave us the classification of râles which has come down to the present with little alteration: "(1) the moist crepitant râle, or *crepitation*; (2) the mucous or *gurgling* râle; (3) the dry sonorous râle, or *snoring*; (4) the dry sibilant râle, or *whistling*; and (5) the dry crackling râle with large bubbles, or *crackling*."

In 1834, Beau¹¹ suggested that the air passing through the glottis was the cause of the respiratory murmur which was modified as it pressed against the walls of the trachea and bronchi and entered the alveoli. He seems to have accepted Laennec's description of the sounds, differing only as to their origin.

Laennec's description of the respiratory sounds and Beau's suggestion as to their origin have been accepted, taught, and described in textbooks until the present time.

Discoveries which carry the mind into fields of thought alien to those prevailing at the time, if not accepted at once, may be lost. Percussion had no outstanding champion until Corvisart took it up 50 years after Auenbrugger had published his discovery. As Corvisart had been obliged to teach himself percussion, so Skoda of Vienna taught himself both percussion and auscultation; and in 1839 published a Treatise on Percussion and Auscultation—78 years after Auenbrugger had published his *Inventum Novum* and 20 years after Laennec's publication on stethoscopic examination of the heart and lungs. Skoda's understanding of auscultation and percussion and the acceptance of it by his pupils may be envisaged by the fact that his book went through six editions between 1839 and 1864. Nevertheless, in spite of the fact that percussion and auscultation received the benefits of the prestige of Corvisart, Piorry, and Skoda, they were slow in receiving general recognition.

But once accepted, the remaining portion of the nineteenth century became distinctly the era of physical diagnosis in diseases of the chest, based on percussion and auscultation. Physicians improved their practice by comparing their findings with the postmortem results furnished by the rapidly

developing school of pathologists, beginning with Morgagni and followed by Rokitsansky and Virchow in the nineteenth century.

In case of the examination of the heart and lungs, in the nineteenth century, inspection gave little direct information to the physician. The use of inspection was confined to the general appearance of the patient and to abnormalities in form and movement. Palpation was confined largely to eliciting the heart-beat, the thrill of murmurs, vocal fremitus, the thrill of large bubbling râles in lung cavities, and large rhonchi, and enlarged glands. Laennec noted that under certain conditions these large râles produce sounds resembling "a drum or a carriage rumbling over a pavement . . . accompanied by a vibration very sensible to the hand and indicative of its proximity."

It was not until after the beginning of the twentieth century that the clinician could use inspection and palpation as major methods of diagnosis of the organs within the chest. By this time the roentgen-ray had been discovered which, while being our greatest single method of examining the chest, has all but proved the fears of those who saw danger to methods of observation in the mechanical wooden stethoscope used by Laennec. However, it must be remembered that mechanical devices can not displace the senses in securing diagnostic data. The patient is an anatomical, physiological and emotional being, in whom departures from normal can be only partly detected by laboratory technics. The mind is necessary to interpret laboratory results and to fit them to the patient's reactions. The more accurate the physical examination made by the clinician the more evident will be the necessity of controlling roentgen-ray findings by data obtained by the eye, the ear, and touch.

When I studied in European clinics in 1894, the wooden monaural stethoscope was in general use, and not infrequently the ear to the chest was used. I do not recall a single European clinician who used a binaural instrument. Percussion was interpreted largely by sound instead of resistance. Different teachers had their own favorite pleximeters, some of wood, others of ivory, and still others of metal. Most, however, appreciated the fact that the best pleximeter was the finger, the differences in perception being of more value than sound. Likewise all kinds of percussion hammers were used—large and small—with little or much rubber on the striking surface. It was taught that light percussion would detect densities near the surface of the chest wall but that heavy blows were necessary for infiltrations deep in the chest. I well remember a professor in Berlin who used finger-finger percussion and could percuss for an entire amphitheater of students, the sound being so loud that it could be heard generally. Such blows throw the entire chest and all structures in the direction of the blow into vibration, cause confusion in interpretation, and may completely obscure the dullness caused by slight pathological changes.

On my first trip to Europe I was instructed in the usual textbook teachings on physical examination, the same as in Cincinnati. However, these were the smallest part of what I learned. I learned something of what the

great men in medicine were doing and thinking, and how they were interpreting their findings in terms of clinical disease. Even with their limited measures they did not hesitate to face the pathologist in case of post mortem.

I heard Senator lecture for one hour on what could be determined of a patient's past illnesses, present condition and future possibilities by inspection. I was more than impressed; I was astounded. How could he see so much, was the question which perplexed me.

In 1895, soon after my return from Europe, I was forced to leave Cincinnati and go to California on account of my wife's illness; and again to leave Los Angeles, our only city in Southern California at that time, with its 60,000 inhabitants, and go to Monrovia, a town of 600 people, in the foothills of the Sierra Madre mountains, because it was a more favorable climate. I had no special knowledge of tuberculosis, but my wife and most of my patients were suffering from it, so I was forced to teach myself. I was particularly anxious to know how to examine chests. I read my textbooks with great care. I tried to apply what I read to the chests that I had to examine. In auscultation I had great difficulty. I could not find the 5-3 or 3-2 ratio of inspiration to expiration given in the books. I found the sounds more nearly equal. I thought I must be wrong. It must be due to my inability to examine, but try as I would I could not make my findings correspond with textbook teaching. It took time for me to think the textbooks were inaccurate, but why should there not be error in textbooks? Everything is not discovered at one time.

One day I put my hand on a patient's back and struck a light blow on the front of the chest—so light that it was scarcely audible—and felt it perfectly through the chest. I then knew that percussion was more delicate than we had believed it to be and began to use a very light stroke—only a tap.

After proving to myself that teachings regarding the relative length of inspiration and expiration were wrong and after demonstrating that a light stroke could be felt clear through the chest, I one day placed my stethoscope over the biceps and noted a sound somewhat like the respiratory sound. I then came to the conclusion that part of the respiratory murmur might be muscular. I was strengthened in this opinion when I listened over the abdominal muscles and heard a murmur, weak but still similar to that often heard over the chest. My confusion was deepening. My own observations were directing me away from my textbooks and teachers.

Further study showed me that inspiration lasts during the entire inspiratory phase of respiration and expiration throughout the entire expiratory phase. It was just one more step to see that the respiratory sounds are caused by all factors in the respiratory mechanism that produce sound vibrations. The strange thing is that it took nearly fifty years after getting my first hint before I was able to take this step and fully satisfy myself that the respiratory murmur is composed of all factors belonging to the respiratory mechanism which are capable of producing sound vibrations.^{12, 13}

It is evident to anyone conversant with the facts of physiology that the respiratory murmur can not be caused by the air rushing through the larynx and dilating the bronchi and air cells, because there is no rushing of air after it enters the trachea. The tidal air which amounts to some 500 to 700 c.c., on entering the air passages, is met by the residual air which nullifies its force. Thereafter the air enters the small bronchi and air cells by diffusion.

If the respiratory murmur is not caused by the action of the air column upon the bronchi and air cells, what would be a satisfactory explanation for the sounds heard in the different lung areas? I suggest that the respiratory murmur is caused by sound vibrations originating in all portions of the respiratory mechanism, and that they vary in quality according to the degree to which the sounds originate in air-containing and non-air-containing tissues.

Non-air-containing tissues are dominant in the upper portions of the lung in the region of the bronchi near the hilum anteriorly and in the inter-scapular space posteriorly. Here large bronchial and vascular trunks and a relatively small proportion of lung tissue are covered by a relatively large mass of musculature and the least elastic portion of the bony cage. Movement is restricted. In this area the murmur has been called *bronchial*. On the other hand, air-containing tissues are dominant in the production of sound in the outer and lower portions of the lungs. Here is a large proportion of pulmonary tissue and the bronchial and vascular trunks are relatively small and covered by a minimum of musculature and the most elastic portion of the bony cage. Here movement is relatively free. In this area the murmur has been called *vesicular*. In the presence of infiltrations the relative amount of non-air-containing tissues is increased, movement is restricted, and so the murmur takes on the so-called bronchial quality.

With this new conception of the respiratory murmur, auscultation becomes a method of studying the respiratory mechanism and the manner in which disease affects changes in respiratory movements and in the production and conduction of sound vibrations. It connects it intimately with inspection, palpation and percussion.

While studying physical examination I put to test my powers of inspection and palpation and tried many different types of percussion. I found that if we depend mostly on sound in percussion, the difference may be exaggerated by striking the chest with many different objects, such as a small rubber tube or a lead pencil. But these were only passing observations. I also outlined organs by palpatory percussion. However, I preferred to interpret percussion according to the sensation conveyed to the finger rather than sound. I learned to feel the effects of the percussion stroke and preferred the fingers for both hammer and pleximeter, using a very light stroke. It was just one more step to detect different densities by palpation, using no stroke at all; and this was soon proved.

At Monrovia I was isolated. I had no access to a library, but I could not get away from Senator's remarkable exhibition of inspection. So when

I began to teach myself to examine a chest, that remarkable lecture of Senator was always urging me to observe.

I could see the difference in movement of the chest wall and thought that differences over an infiltrated area as compared with a normal chest should also be felt. I palpated as well as percussed. After 14 years' trial I found that there was something felt over pathologic chests which was not noted over normal chests. Then one day I made an unexpected but important observation.

I was examining a patient who had marked infiltration at the right apex, with adherent pleura. Palpating over the first intercostal space I found a resistance greater than normal. I attributed it to the muscles. They seemed to be in spasm. I persisted and a few months later^{14, 15, 16, 17, 18, 19} was able to demonstrate not only an increased density in the lung but a muscle spasm as well. I believed that I had observed the same spasm in inflammation of the lung as is found in appendicitis, inflammation of the gall-bladder and gastric ulcer.

I followed this lead carefully. I began to look for muscle tension in every patient whom I examined, and after a short time found that the lungs reflect in the muscles of the shoulder girdle—the sternocleidomastoideus, scaleni, levator anguli scapulae, acromial portion of the trapezius—and the crus and central tendon of the diaphragm. I found that all those muscles that are visible show spasm when the disease is active and degeneration when it is chronic or healed. I assumed that the same is true with the crus and central tendon of the diaphragm.

I also felt that it was not possible that the lessened motion on the side of the diseased lung in early cases could always be caused by the small infiltration present. I assigned it partly to the effect of spasm of the sternocleidomastoideus and scaleni above and the crus and central tendon of the diaphragm below interfering with the respiratory movement.

In my first observation I probably was feeling both the density of the underlying infiltrated pulmonary tissues and the spasm of the intercostal muscles caused by the underlying pleura. But the important fact was that I recognized increased tension and so persisted until I had found both the pulmonary and pleural reflexes and was able to differentiate them by the segments of the cord in which they were mediated, and had proved the ability to outline the heart and detect densities in the lungs by palpation.

I soon found that the muscles of the shoulder girdle and the crus and central tendon of the diaphragm receive their nerve supply from the mid-cervical segments of the spinal cord, particularly the third, fourth and fifth, and the pleura from the thoracic segments.

Sometimes, when active tuberculosis is present, one can see the muscles standing out in increased tension, but it is detected better by palpation. One can also see the lessened motion of the hemithorax which I have suggested might be partly caused by spasm of the sternocleidomastoideus and scaleni

above and the crus and central tendon of the diaphragm below. Aside from the spasm I found that the muscles, subcutaneous tissue and skin innervated by nerves from these same cervical segments show atrophy when the disease in the lung has become chronic or healed, and the skin and subcutaneous tissues overlying acute pleurisy atrophy when the pleural inflammation continues for any length of time.

The pleural motor reflex as shown in the intercostal muscles seems to be coextensive with the pleural inflammation. Both pleural motor and trophic reflexes are produced by the intercostal nerves which mediate in the same thoracic segments of the cord that receive the afferent impulses from the pleura.

The pleural trophic reflex, like the pulmonary trophic reflex, is of great importance diagnostically. It is not possible to differentiate the reflex pleural atrophy of the intercostal tissues from the degenerations which Coplin²⁰ has described as being caused by direct extension of the pleural inflammation to the intercostal structures; in fact, they are probably the same.

Inflammation in the lungs and pleura is easily differentiated reflexly because the pulmonary motor reflex is expressed in the muscles of the shoulder girdle (the accessory muscles of respiration) and the diaphragm; and the pleural motor reflex in the intercostal muscles. The atrophy caused by inflammation in the lung, aside from that in the muscles, involves the skin and subcutaneous tissues above the second rib anteriorly and the spine of the scapula posteriorly, while atrophy from pleural inflammation may involve the intercostal structures and subcutaneous tissues of the chest anywhere below the second rib anteriorly and the spine of the scapula posteriorly.

Our knowledge of the pulmonary and pleural reflexes offers aid in interpreting râles. While squeaks and wheezes are definitely signs of bronchial obstruction, the so-called moist râles are not so easily interpreted. They are not always caused by moisture in the air passages, nor are they always indicative of the presence of active tuberculosis when heard at the apex following a quick inspiration after exhalation and cough, as usually taught.

Râles which can not be differentiated from the so-called moist râles may be heard over the areas of pleural atrophy. Although at or near the apex they can not be differentiated from pulmonary râles, over the lower portion of the thorax their nature is more definite. Like the râles in tuberculosis, they are not always present. They are frequently found in patients with a history of previous pleurisy with effusion. I have known them to persist for years—in one case more than 40 years. The presence of the pleural trophic reflex without the pulmonary motor reflex is the key to the diagnosis. The roentgen-ray may show no pulmonary involvement, and there may be no history of recent pulmonary disease. The patient may complain of pain, for which a diagnosis of intercostal neuralgia is often made.

The discovery of the reflexes from the lung permitted me first to point out the important physiologic fact that while the lung receives its sympathetic

nerve supply from the upper five or six thoracic segments, the midcervical segments of the cord contain the centers in which the afferent nerves which course in the pulmonary sympathetic system mediate reflexes in the somatic structures—muscles, skin and subcutaneous tissues. In order to do this, stimuli must be conveyed from the lung to the upper thoracic segments, thence upward over intracentral paths to the midcervical segments, thus differing from other important viscera.

The pleural reflexes follow Sherrington's law²¹ to the effect that each afferent impulse finds in the segment of the cord which it enters an efferent neuron with which it will mediate a reflex most readily; but to explain pulmonary reflexes it was necessary to suggest a modification of this law²² as follows: *Each afferent impulse from the lung finds in that segment of the cord with which it is embryologically connected an efferent neuron with which it will unite most readily to produce reflex action.*

I also found that the afferent fibers in the vagus of the parasympathetic nervous system mediate with efferent neurons of the cranial nerves in case of the facial muscles, the Vth, VIIth and IXth in case of the tongue. The atrophy of the facial structures and tongue is best seen in chronic largely one-sided destructive pulmonary lesions and sometimes following thoracoplasty.

While pursuing the study of these reflexes, I one day (as previously stated) noted that I could detect the borders of the heart by palpation. It did not seem possible that an organ deep within the chest cavity could be felt. But by continuing my search I found that I could not only outline the heart by palpation but I could detect the difference between the density of normal lungs, infiltrated lungs, and distended lungs such as we find in asthma and emphysema. This could be detected by pressure so light that it barely indented the skin, so I called the method *Light Touch Palpation*.^{16, 23} This gives a new method whereby one by palpation can outline the heart and differentiate various pathologic conditions in the lung and pleura by differences in density. Furthermore, it proves the validity of very gentle percussion.

During the nineteenth century physical diagnosis of organs within the chest was based only on percussion and auscultation. In the twentieth century, now that the reflexes from the lung and pleura have been described and the ability to palpate structures—both superficial and deep within the chest—has been discovered, physical examination becomes more accurate, and inspection and palpation assume major importance.

Physical examination of the organs within the chest has now been enriched, and the physician has at his command methods as accurate as his perception and interpretation of sight, hearing and touch can make them. Whether the disease is active or inactive can be determined by sight and touch. Furthermore, findings can be studied in connection with roentgenograms of the chest which afford a valuable method of recording the living pathology of these structures.

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CHRONIC LEUKEMIA OF LONG DURATION: WITH A REPORT OF 31 CASES WITH A DURATION OF OVER FIVE YEARS *

By HERBERT C. MOFFITT, JR., M.D., and JOHN H. LAWRENCE, M.D., D.Sc.,
Berkeley, California

Numerous physicians have observed cases of leukemia of unusually long duration, but there is no published summary of many such cases. An analysis of unusual cases might add to knowledge of leukemia as a whole. Also if one could determine what factors lead to an unusually long duration, prognosis would be easier and therapy could be evaluated more readily. It therefore seems worthwhile to review the literature as it pertains to cases of leukemia of long duration and to select a group of such cases, from those seen by us, for analysis.

DETERMINATION OF DURATION

The determination of duration presents a problem in a disease with an onset as insidious as that in leukemia. Most published reports have estimated duration from the onset of symptoms, but it is often difficult to date the beginning of such vague symptoms as weakness, easy fatigability, or general malaise. Minot and Isaacs²⁵ estimate that in 100 cases of chronic myelogenous leukemia an average of eight months passed between the onset of symptoms and the first visit to a physician, whereas in 72 cases of the chronic lymphatic type a nine months period elapsed. Widmann⁴⁰ considers that duration should be calculated from the date of diagnosis, which is known, rather than from the date of onset of symptoms.

The actual disease process may antedate the onset of symptoms by a considerable period. It is well known that chronic leukemia may be detected from routine examination of the blood prior to the onset of any symptoms.³⁴ Wintrobe and Hasenbush⁴¹ estimate that two to five years—or longer—elapse between the actual time of onset of chronic myelogenous leukemia and the time when symptoms cause the patient to seek medical aid. In chronic lymphatic leukemia they⁴¹ found that one and a half to two and a half years passed between the finding of signs of the disease (leukocytosis, glandular enlargement, or splenomegaly) and the development of symptoms of the disease. They believed lymphatic leukemia was discovered earlier in its course because of the associated lymph node enlargement.

Table 1 summarizes the average duration of cases of chronic leukemia as recorded in various reports. A notation is made as to what date was used

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From the Radiation Laboratory, the Division of Medical Physics and the Division of Medicine, Donner Laboratory of Medical Physics, University of California.

TABLE I
Average Duration of Cases of Chronic Leukemia in Years

Author	Duration Calculated from	Myelogenous			Lymphatic		
		No. Cases	Average Duration	Per cent >5 yrs.	No. Cases	Average Duration	Per cent >5 yrs.
Arendt and Gloor ¹ Bethell ²	Onset symptoms	39	4.3		22	4.2	
	Onset symptoms				52	0.33	
					(lymphoblastic)		
					70	2.6	
Hoffman and Craver ¹¹	Onset symptoms	82	3.36		(lymphosarc. cell)		
	Beginning of treatment				68	4.85	
					(lymphocytic)		
Jackson ¹⁶	Onset symptoms			10			10
Lawrence et al. ^{14, 16a}	Onset symptoms	127	4.0+	30	100	4.5+	32*
Leavell ¹⁷	Onset symptoms	87	3.2	20	49	3.6	20
Leucutia ²⁰	Onset symptoms	18	3.3		13	4.33	
Minot ^{24, 25}	Beginning of treatment	18	2.1		13	2.5	
	Onset symptoms	52	3.04		80	3.5	14
		(non-irrad.)					
		78	3.5	12	7	1.07	
Pascucci ²⁸	Onset symptoms	64	2.5	5	(Aet. < 30)		
Reinhard ²¹	Onset symptoms	21	3.64		64	2.8	14.5
		(P ²² treated)					
Widmann ⁴⁰	Beginning of treatment	25	2.7		24	3.3	
Wintrobe and Hasenbush ⁴¹	Date diagnosis	23	1.68		23	1.07	
Wintrobe ⁴²	Onset symptoms	23	2.79		23	2.33	
	Onset symptoms	259	3.28		152	3.29	

* Many patients in both the lymphatic and myeloid groups are still alive—and it seems certain that the eventual figure for average duration will be five or more years.

by the authors in calculating duration wherever this information was ascertainable. Arendt and Gloor¹ described a small series of cases treated with arsenic and roentgen-ray. They did not give statistics but data calculated from their graphs show that their patients had a longer average duration than usual. This finding may have been related to the treatment given, or may simply be due to the small number of cases described. Bethell's review² of cases of chronic lymphogenous leukemia shows a longer duration of the lymphocytic type than is usually observed because he separated these from the lymphoblastic and lymphosarcoma cell types and because he obtained a good follow-up of most cases seen at the Simpson Memorial Unit of the University of Michigan. Sturgis³⁵ excluded cases of lymphosarcoma cell leukemia from cases of true chronic lymphatic leukemia when calculating duration. Lawrence et al.^{16a} did not exclude these cases, yet they found also a relatively long duration and 22 of their patients are still living, so the average figure will be increased further. No significant difference was observed

between males and females with regard to duration of life in Hoffman and Craver's review.¹¹ Minot and Isaacs²³ noted that the age at which the disease occurred did not seem to affect the duration of chronic myelogenous leukemia but was a definite factor in the chronic lymphatic type where the disease apparently lasted a shorter time under the age of 40 years, and particularly under 30, than it did when it occurred between 40 and 60. Leavell's review¹⁷ gave him a similar impression. Lawrence et al.¹⁶ concluded that there were no remarkable differences in duration of the disease with various ages of onset in their series of 129 cases of chronic myelogenous leukemia but observed in the case of chronic lymphatic leukemia^{16a} that the prognosis was better in the 30 to 40 age group. Widmann's report⁴⁰ deals with 49 patients who were treated and followed at the Philadelphia General Hospital. Patients with leukemia who were too ill to be treated, were not treated, or were not adequately followed, are excluded. The data by Wintrobe⁴² represent cases previously reported by various writers and probably include cases listed elsewhere in table 1.

PARTICULARLY LONG

Several reports are worth special mention because they describe cases of particularly long duration. These are summarized in table 2. Miller and Turner²³ emphasize the wide variation in life span seen especially in chronic lymphatic leukemia and state that an occasional patient may live 25 years with the disease. They may have had reference to McGavran's case.²² Widmann⁴⁰ includes two patients with lymphogenous leukemia of 13 and 18 years' duration and two with the myelogenous type of 13 and 19 years' duration in his report of 49 cases. He attributed the unusually long duration of these four cases to the existence of a benign type of the disease rather than to any effects of treatment. Fowler⁶ states that rare instances in which

TABLE II
Cases of Chronic Leukemia of Particularly Long Duration

Author	Type	No.	Years Duration	Duration Calculated from	Treatment
Craver ⁴	Lymphatic	1	12 or 13	Onset of symptoms	X-ray
Forkner ⁵	Myelogenous	1	18	Date of diagnosis	None
Hoffman and Craver ¹¹	Myelogenous	4	11, 12.5, 16, 16.5	Onset of symptoms	Only during last 1 to 14 years
Jackson ¹⁴	Lymphatic	2	10, 12	Date of diagnosis	X-ray
Leavell ¹⁷	Lymphatic	1	16	Date of diagnosis (14g then 45%)	
Lawrence et al. ¹⁶	Myelogenous	3	9,* 10*	Onset of symptoms	P ³² alone or with x-ray
Lawrence et al. ^{16a}	Lymphatic	4	20,* 12,* 12,* 11	Onset of symptoms	P ³² alone or with x-ray
McGavran ²²	Lymphatic	1	25	Date of diagnosis	X-ray during last 15 yrs.
Minot and Isaacs ²³	Lymphatic	3	11, 15, 22	Date of diagnosis	No irradiation
Richards and Moench ⁴⁰	Lymphatic	1	16	Date of diagnosis	None
Rosenthal ⁴⁰	Myelogenous	1	16		
Widmann ⁴⁰	Lymphatic	2	13, 18	Date of diagnosis	X-ray
	Myelogenous	2	13, 19	Date of diagnosis	X-ray

* Patient still living.

chronic myelogenous or lymphatic leukemia has been present for 15 to 20 years have been recorded but that this exceedingly benign form is not common. Forkner⁵ had a patient with chronic myelogenous leukemia who showed a white blood cell count of about 30,000, with many myelocytes and myeloblasts, for 18 years without any specific treatment. Lawrence et al.^{16, 16a} have several patients with very long duration now under observation.

REMISSIONS

In the course of leukemia, remissions, both symptomatic and hematologic, may occur spontaneously as well as from the effects of treatment. Such spontaneous remissions may contribute to the long duration of many of the unusual cases under discussion but no cause—other than natural variation in the disease—has ever been definitely established for their occurrence. Forkner⁵ states that patients may frequently remain in a more or less stationary phase for several years but that complete spontaneous remission has never been recorded in chronic leukemia. Minot and his associates^{24, 25} described spontaneous remissions of moderate degree in 7.7 per cent of their series of patients with chronic myelogenous leukemia and 5 per cent of cases with the chronic lymphatic variety. None of these patients had been irradiated. Sturgis²⁶ estimates that spontaneous remissions occur in less than 10 per cent of patients with chronic myelogenous leukemia. Pierce,²⁹ Marcus,²¹ and Whitby and Christie³⁹ have also described cases with remissions of varying duration and completeness. Jackson^{11, 12, 13} has described two cases of temporary complete remissions, both clinical and hematological, in acute leukemia, each lasting five months. One remission followed the administration of yeast adenylic acid and the other followed the administration of pentnucleotide to a child who had developed otitis media and lip necrosis as complications of measles and acute lymphatic leukemia, but both were considered to be of spontaneous origin. Moeschlin²⁷ has been quoted by Bethell et al.³ as reporting several unusual remissions in myelogenous leukemia. In one of his cases three remissions occurred in the 16 month course of one case and the marrow obtained by sternal puncture appeared normal during a remission. The remission in Rappoport and Kugel's case³⁰ of monocytic leukemia is also noteworthy because of serial marrow examinations. On first examination, the marrow suggested leukemia. During remission the marrow differed but slightly from normal and the previous provisional diagnosis of leukemia could not be substantiated. Subsequently the marrow became characteristic of monocytic leukemia and the patient died of the disease.

EFFECTS OF INFECTION

Various types of infection have been reported as a cause of remission in leukemia. Infection might, therefore, be a factor in cases of long duration. Forkner⁵ reviewed the pertinent literature and concluded that, although many miscellaneous infections were associated at times with evidences of

regression, in all instances in which recovery from infection occurred leukemic manifestations recurred, usually in a few weeks. Wintrobe and Hasenbush⁴¹ stated that "contrary to the opinion frequently expressed, infections in the great majority of the cases did not produce a remission in the physical signs or in the blood picture." In four of their cases, infections actually caused an increase in white blood cell count. Heinle and Weir⁹ describe the morphologic obliteration of a case of chronic myeloid leukemia by active tuberculosis and discuss the inter-relations of leukemia and tuberculosis. The relationships of these two diseases are also discussed by Ulrich and Parks.³⁶

EFFECTS OF TREATMENT

It is generally agreed^{11, 15, 16, 16a, 20, 24, 25, 26, 40} that there is not yet clean cut evidence that treatment has significantly prolonged the duration of any type of chronic leukemia. However, practically all agree that radiation therapy lengthens the period of comfortable and useful life. The possibility of cure of leukemia is still undetermined. Until more is known about the etiology of leukemia, it can not be stated definitely whether recovery is possible. Certain conditions may simulate leukemia. Washburn³⁸ treated a case of chloroma with excision and radiation. The patient showed myeloblasts and myelocytes in the blood and lesions in bones other than the one removed surgically. The patient was well two and a half years after the operation. This case was reviewed in 1941 by Washburn and Christie³⁵ at the completion of 15 years of follow-up. At that time the patient was in fairly good general health, had normal bones on roentgen-ray examination, and exhibited no blood abnormalities. The authors concluded that it was impossible to say whether the patient had either xanthoma or chloroma. One can therefore not accept this case as a cure of leukemia. Lecène¹⁹ is quoted by Forkner⁵ as reporting a possible two year cure of a case of localized chloroma. Lebon¹⁸ and Schiassi³⁴ each reported cases cured or long-arrested by roentgen radiation according to Forkner.⁵ Herz¹⁰ recorded the case of a physician of 27 who apparently recovered from acute leukemia. The patient exhibited malaise, fever, ecchymoses, necrotic tonsils, cervical and axillary adenopathy, and splenomegaly. Hemoglobin was reported 85 per cent, red cell count 4.5 million, platelets reduced, and white cell count 18,000, with 50 per cent myeloblasts. The author evidently believed mononucleosis was ruled out by differential staining reactions but unfortunately the case preceded the development of the Paul-Bunnell test. The sternal marrow was evidently not examined. Herz concluded that acute leukemia was not necessarily fatal and that the diagnosis need not be discarded if the patient recovered. Gloor⁷ has reported the case of a 49 year old businessman who had fever, swollen, ulcerated, bleeding gums, enlarged tonsils and cervical nodes, hepatomegaly and splenomegaly, anemia (hemoglobin 51 per cent, red blood cells 2.76 million), and a white blood cell picture of acute

leukemia (white blood cells 15,800 with 91 per cent myeloblasts) when first seen. After therapy with roentgen-ray, arsenic, intravenous mesothorium, transfusions, and iron, a marked leukopenia (white blood cells 955) developed and myeloblasts disappeared from the peripheral blood. Two months later the blood picture was normal and it remained so two years later although slight splenomegaly persisted. Platelet counts were not discussed and the sternal marrow was apparently not examined.

Minot's patient²⁶ exhibited anemia, thrombopenia, and a leukocyte pattern indistinguishable from acute leukemia but recovered without special treatment. The case is recorded in detail and should be acceptable as a cure if any case of leukemia is to be recognized as cured, but Minot describes it as a case "simulating" leukemia with recovery.

These and other reports of alleged cures of leukemia were reviewed by Forkner.⁵ He believed that only a few of the reported cases had been studied adequately for evaluation but that a few patients who presented a picture identical with that of leukemia had recovered. Moeschlin,²⁷ quoted by Bethell et al.,³ however, concluded that "a critical review of the literature fails to disclose a single well-authenticated case in which leukemia was actually cured."

PROGNOSIS

Pascucci²⁸ summarized the factors which were associated with short duration of the disease in his series of 128 patients from the Presbyterian Hospital in New York. He listed the following findings as indicating a poor prognosis, but stated there were few substantiating statistics: very high or very low white blood cell count, serious anemia, high number of blast cells, excessively high or excessively low platelet count, marked splenomegaly, diffuse lymph node involvement, presence of complications (hydrothorax, pneumonia, tuberculosis, osteomyelitis, cardiovascular disease, etc.) and short duration of symptoms prior to diagnosis. It was suggested that the patients with a short duration of symptoms prior to diagnosis had a less chronic form of the disease.

Leavell¹⁷ discussed several factors affecting the prognosis at the original examination. The prognosis was better in chronic lymphatic leukemia with onset between the ages of 40 to 60 years but seemed unaffected by age of onset in chronic myelogenous leukemia. The presence of anemia led generally to a poor prognosis, particularly in lymphatic leukemia, but one patient was mentioned who lived 16 years after being seen with a hemoglobin of 45 per cent. The height of the leukocyte count was of some prognostic significance in that patients with myelogenous leukemia tended to do poorly if they originally showed a relatively low white cell count whereas those who had lymphatic leukemia lived somewhat longer if the original leukocyte level was relatively low. Bleeding manifestations at the original examination were usually associated with short duration of the disease.

Lawrence and his co-workers^{16, 16a} observed that it was not possible to predict which patients would have a long duration of their disease but that since with present methods of treatment over one third of these patients survive five years or longer, it must be assumed by the physician that any individual patient under treatment will fall into this group. Actually the five year survival figures are good when compared to those of cancer of the esophagus, stomach and lung, and many other neoplasms in the more advanced stages.

PARTICULARLY CHRONIC FORM

Many authorities have "explained" the long duration of certain cases of chronic leukemia by assuming that there exists a particularly chronic form of the disease. To state that cases of long duration have a long duration gives no real explanation for the phenomenon, nor does it help us to select in advance those cases which will eventually turn out to belong to the particularly chronic variety. Haden⁸ has noted that chronic lymphoid leukemia is often very mild and runs a benign course. Minot and his co-workers stated²⁴ that "many . . . patients had symptoms for a long time prior to therapy and were recognized as having the type of case that progressed sluggishly." Pascucci²⁸ wrote: "Chronicity, measured by the duration of symptoms before the patient seeks medical aid, has a definite bearing on survival: the more chronic the disease, the longer is the life expectancy." He showed the following survival periods in relation to duration of symptoms before treatment.

Duration Symptoms Before Treatment	Myeloid		Lymphatic	
	Years	Patients	Years	Patients
6 months	2.2	31	1.8	18
6 months to 1 year	2.3	11	2.3	18
1 to 2 years	3.1	5	2.7	11
2 years or over	3.9	5	5.0	12

Widmann⁴⁰ stated: "The four instances in this series (vide supra) of an unusually long life may be the effect of a very benign character of the disease and not attributable directly to irradiation."

CASE REPORTS

From a total of approximately 190 cases of chronic myelogenous and chronic lymphatic leukemia seen and treated at the Crocker Laboratory since 1937, we have selected 31 cases of particularly long duration for presentation. With the passage of time the number in this group will become larger since many of these patients have been first seen during the past few years. The patients selected were those who had lived five years or more after the diagnosis had been established by blood counts.

The much larger group of patients living five years after onset of symptoms was not included. These cases are summarized in tables 3 (Chronic Lymphatic) and 4 (Chronic Myelogenous Leukemia). It is of interest that two-thirds of our patients with myelogenous leukemia who lived over five years from the date of diagnosis were women whereas there was only one woman in our series of long-lived patients with lymphatic leukemia. These findings suggest that a hormonal factor may be operative in some patients with long duration. In our experience approximately 70 per cent of patients with lymphatic leukemia are males and 60 per cent of those with myelogenous are males. With the passage of time the number of patients in this series will increase.

The age of onset is tabulated in the third column of tables 3 and 4. The average values correspond with Minot's findings^{24, 25} and that of our complete series^{16, 18a} for the age incidence of leukemia but there is considerable individual variation. As stated above, in our patients with lymphatic leukemia those with onset between the ages of 30 to 40 have the longest duration.

The seven patients in table 3 and three patients in table 4 whose age at death is not recorded in column four were alive at the time of writing this report (May, 1948). All 10 were doing very well at the last examination. Six in the lymphatic group and two in the myelogenous group have had no treatment for two or more years.

Duration of the disease is listed in the next three columns of both tables. The date used for onset of symptoms was that from which symptoms could be definitely attributed to leukemia. Some patients gave histories of vague or general symptoms preceding the actual date used but these were disregarded in the interests of accuracy. The next eight columns tabulate the earliest findings now available to us. As noted in the first column of this section, the original blood counts on which the diagnosis was based are not available to us in every case but where they are not, the time interval which elapsed between diagnosis and the first count recorded in our records is noted. In accord with Pascucci's²⁶ and Leavell's¹⁷ lists of factors affecting prognosis which have been referred to above, it will be noted that few of the patients who lived long with lymphatic leukemia had significant anemia at the onset but case JFP, who is now alive with normal total blood cell counts, had a significant degree of anemia 11.6 years ago. More marked anemia was a common early finding in the group of the myelogenous type.

Original white blood counts varied widely but there were none with leukopenia and none higher than 300,000 in the lymphatic or 500,000 in the myelogenous groups.

Abnormal differentials were of course present at the original examination which established the diagnosis but the per cent of immature cells in the myelogenous series was low and few of these abnormal cells were blasts. This was another factor of prognostic significance which Pascucci listed.²⁸

Splenomegaly was marked at the onset of three of the myelogenous cases and lymphadenopathy marked from the beginning in four of the lymphatic cases. These findings are ordinarily thought to connote a poor prognosis. In several cases the early physical findings were not reported to us.

Three columns in each table list the treatment given to these patients throughout the course of their illness. The treatment in most of these cases has been so varied that an analysis of its effect on duration would not be of value. Although our treatment has been chiefly with radioactive phosphorus (P-32) occasionally supplemented with roentgen-ray, a few of these patients had been treated previously with roentgen-ray or Fowler's solution while not under our supervision. The total dose of P-32 given (column 16) accordingly depends more on how long the patient was under our immediate supervision than it does on the severity of his leukemia. It is of interest, however, that eight patients (four with lymphatic and four with myelogenous) who lived five years or more after the diagnosis of leukemia were treated with radioactive phosphorus only.

TABLE III
Chronic Lymphatic Leukemia

Case	Sex	Age		Duration in Years from			Early Findings						Treatment			Late Findings									
		Onset Symptom.	Death	1st Sympt.	Diag.	1st Rx.	Years after Diag.	Hg %	RBC $\times 10^6$	WBC $\times 10^3$	% Abn. Lymph.	Spleen	Liver	Nodules	pos. me.	N. ray Courses	Orchi	Years after Diag.	Hg %	RBC $\times 10^6$	WBC $\times 10^3$	% Abn. Lymph.	Spleen	Liver	Nodules
FAB	M	39	—	7.6	7.6	7.5	0.0	82	4.50	148	96	0	0	Slt.	30	2	0	7.6	90	4.34	17	90	0	0	Slight
FMB	M	56	67	11.2	10.5	10.4	0.0	80	5.01	39	94	Mod.	0	Mod.	27.3	2	0	8.7	72	3.74	18	89	Mkd.	0	Mod.
AB	M	49	57	7.8	5.8	5.8	0.0	80	4.55	53	95	*	*	Mkd.	11.9	2	Fowler's	5.0	84	3.74	18	75	Slight	0	Mkd.
BC	M	34	40	6.6	6.3	3.7	0.0	97	4.94	34	64	Mod.	*	Mkd.	30.9	0	0	6.6	25	1.15	71	99	*	0	0
LPD	M	50.3	—	19.7	19.0	19.0	4.0	100	5.09	70	98	Slt.	0	0	18.5	Many	0	19.0	92	5.42	19	85	0	0	0
FPE	M	40	—	5.3	5.3	5.3	0.4	87	4.18	21	81	*	*	Mod.	8.8	1	Fowler's	5.3	110	5.10	14	69	*	*	*
KCG	M	36	42	5.4	5.4	1.5	0.0	*	*	46	*	*	*	Mkd.	7.4	2	0	5.4	69	3.89	22	90	*	*	Mkd.
GEH	M	66	73	7.9	7.9	7.9	0.0	81	4.28	170	95	Slt.	*	Slt.	52.8	Many	Benzine	7.8	47	2.30	73	94	*	*	Mkd.
FHL	M	65	74	9.0	9.0	7.0	0.0	*	*	20	60	*	*	0	28.4	2	Fowler's	9.0	60	2.75	14	76	*	*	0
FWL	M	55	62	7.3	6.8	6.8	0.5	107	5.62	43	77	0	0	Mod.	48.1	1	Fowler's	6.8	*	2.00	246	97	Slight	0	Slight
JFP	M	35	—	11.6	11.6	11.5	0.0	70	3.17	21	90	0	0	0	10.0	0	Fowler's	11.6	104	4.86	9	68	0	0	0
MP	F	59	—	7.2	7.2	7.0	0.2	90	5.56	92	81	Slt.	0	Slt.	22.7	0	0	7.2	98	5.09	30	81	0	0	Slight
BJP	M	54	—	6.0	6.0	6.0	1.5	90	4.68	294	96	Slt.	0	Mod.	42.8	0	0	6.0	45	4.70	26	57	0	0	Slight
CWR	M	50	55	5.4	5.4	5.4	0.0	*	*	25	*	*	*	*	19.2	Many	*	5.2	30	1.65	331	*	*	*	0
CRR	M	43	49	6.3	6.3	6.3	0.0	70	3.65	115	94	Mkd.	*	Mkd.	17.4	Many	Fowler's	6.3	*	*	21	*	*	*	0
CLS	M	37	—	11.6	10.6	7.8	0.0	110	5.27	18	70	Slt.	Slt.	Mod.	23.0	0	0	8.3	104	5.16	23	78	Slight	0	0
Av. 15 M		48	57.7	8.44	8.16	7.4		88	4.67	93	85							7.86	76.4	3.73	64.8	82			

* Seen elsewhere—Data not available.

Followed by other M.D. or clinic—Data not available.

TABLE IV
Chronic Myelogenous Leukemia

Case	Sex	Age		Duration in Years from			Early Findings							Treatment				Late Findings							
		Onset Sympt.	Death	1st Sympt.	Diag.	1st Rx	Years after Diag.	Hg %	RBC $\times 10^6$	WBC $\times 10^6$	% Abn.	Spleen	Liver	Nodes	pa me.	X-ray Courses	Other	Years after Diag.	Hg %	RBC $\times 10^6$	WBC $\times 10^6$	% Abn.	Spleen	Liver	Nodes
1A	F	49	54	5.5	5.1	5.0	0.1	48	2.96	455	31	Mod.	*	*	26.0	Many	0	5.0	66	3.20	86	22	Mod.	Mod.	0
DEF	F	35	40	5.3	5.3	4.4	0.0	54	3.10	305	15	Mkd.	0	0	14.3	Many	0	5.3	47	2.46	136	53	V. Mkd.	Mod.	0
MG	M	39	45	5.9	5.9	5.3	0.0	70	3.80	35	8	0	Slight	0	50.0	Many	Fowler's	5.9	70	3.09	82	47 (blasts)	V. Mkd.	Mkd.	0
FG	F	20	26	6.0	6.0	6.0	3.5	76	4.39	94	*	Mkd.	*	*	7.0	Many	Fowler's	6.0	73	3.67	9	30	#	#	#
EH	M	32	36	6.0	6.0	6.0	3.0	57	3.43	249	45	Mkd.	*	*	13.0	Many	0	6.0	75	3.60	46	28	Mkd.	#	#
MLI	M	43	—	5.6	5.6	3.8	0.0	90	4.60	228	40	Mkd.	Slight	0	23.7	0	0	5.6	80	4.35	17	12	Slight	0	0
IJ	F	44	—	6.8	6.6	6.6	0.0	68	3.40	110	17	Mod.	Slight	0	58.6	0	0	6.6	86	3.68	68	11	Mod.	Slight	0
WOJ	F	29	35	5.2	5.0	4.9	0.0	70	3.72	127	24	0	0	0	43.6	0	0	5.0	30	1.0	100	#	#	#	#
CK	M	27	36	9.0	9.0	8.8	0.2	86	3.42	200	20	Mod.	Slight	0	40.1	Two	0	8.8	60	3.65	13	69	Mkd.	#	#
ALV	F	52	60	8.8	7.6	7.2	0.4	75	3.13	208	33	Slt.	Slight	0	42.9	Many	0	7.6	56	3.13	11	50 (blasts)	Slight	0	0
PPM	F	11	—	8.3	8.3	8.1	0.0	87	4.75	65	39	Mod.	0	0	22.9	0	0	8.3	97	4.84	11	1	0	0	0
JM	F	55	59	6.3	6.3	6.3	0.0	*	*	268	15	*	0	0	77.4	Many	0	6.3	59	3.25	145	33	Mod.	Mod.	#
MGM	M	26	32	5.5	5.5	5.5	3.0	80	4.00	310	*	Mod.	0	0	19.5	Many	0	5.5	85	4.47	26	16	Mod.	0	0
THM	F	53	50	6.8	6.8	6.6	3.4	*	*	30	10	Slt.	*	*	1.1	Many	0	6.8	39	2.04	17	50 (blasts)	Mod.	Slight	0
EP	F	32	38	6.0	6.0	6.0	4.5	90	4.55	20	13	*	*	*	10.5	Many	0	6.0	34	1.97	0.8	#	#	0	0
Av. 10F = 67% 5M = 33%		36.3	43.3	6.47	6.33	6.03	—	73	3.79	180.8	23							6.3	63.8	3.23	51.2	34			

* Diagnosed elsewhere—Data not available.

Followed elsewhere—Data not available.

The last eight columns in each table list the latest findings available in each case. It will be noted that many patients developed anemia terminally, as one would expect, but that a number were alive with very satisfactory blood counts many years after their diagnosis was first made. Seven of the myelogenous group developed terminally an acute phase with fever, gastrointestinal disturbances, and many myeloblasts in the peripheral blood. This is a common terminal picture in chronic myelogenous leukemia.

Four patients have exhibited prolonged remissions following treatment. In two patients (MLI and PM, table 4) with myelogenous leukemia these remissions were characterized by the complete absence of abnormalities on physical examination and by normal total blood counts, although an occasional myelocyte could be found in blood smears, for three years.

Infection has apparently played no part in the long duration of these cases. Repeated blood examinations have shown no constant changes of significance during the course of intercurrent infections. Two patients with the lymphatic type (FAB and BC, table 3) have each had pneumonia on two occasions without any definite change in the leukemic process. One patient (FWL, table 3) made a satisfactory recovery following appendectomy for acute appendicitis and another (JM, table 4) recovered from cholecystitis and cholelithiasis after cholecystectomy with no apparent alteration in their leukemia. In passing, it is of interest to note that recently we have had develop a complicating carcinoma of the uterus in a 60 year old woman with chronic myelogenous leukemia, under treatment for over five years. Now three months after hysterectomy, this patient is normal physically and hematologically and only after careful search can a rare myelocyte be found in the blood smears.

SUMMARY

The literature of chronic leukemia of long duration is reviewed and 31 such cases treated and observed by us are reported and analyzed. It is concluded that many patients with this disease respond well to treatment and have relatively long comfortable lives.

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PRIMARY CARCINOMA OF THE LIVER— 25 YEAR STUDY *

By G. F. STRONG, M.D., H. H. PITTS, M.D., and J. G. MCPHEE, M.D.,
Vancouver, B. C.

IN 1932 Drs. Strong and Pitts¹ presented in detail 12 proved cases of primary carcinoma of the liver. Only those cases confirmed by necropsy and by microscopic examination of sections of the liver were included. These cases consisted of 10 Chinese and two whites, all of whom were males, seen on the wards and examined post mortem at the Vancouver General Hospital during the years 1920 to 1931 inclusive. The present report contains the findings of 43 additional cases seen in the same hospital from 1932 to 1944 inclusive. Thus, altogether this is an analysis of 55 proved examples of primary hepatic malignant disease seen during a 25 year period.

TABLE I
Analysis of 55 Cases of Primary Carcinoma of Liver

	White		Chinese		Japanese		Total
	M	F	M	F	M	F	
Previous report 1920-1931	2		10				12
Present report 1932-1944	15	1	25		2		43
Total, 1920-1944 inc.	17	1	35		2		55
			Hepatoma	41			
			Cholangioma	14			

Of the 43 new cases being discussed (table 1), 25 are Chinese males, two are Japanese males, 15 are white males and one is a white female. When these are added to those previously reported, the final totals are 35 Chinese males, two Japanese males, 17 white males and one white female. There would appear to be an increasing incidence among whites, for in the first report whites comprised only 16.6 per cent of the cases, and in the total series the percentage of whites had risen to 37.2 per cent of all cases. It is to be noted that as in other series the finding of primary carcinoma of the liver in white women is very rare. The occurrence of a large number of cases of primary carcinoma of the liver in Chinese men without any in Chinese women is probably not significant since we see very few Chinese women in the Vancouver General Hospital.

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The present series of 43 cases consisted of 33 hepatomas and 10 cholangiomas, and when these are added to those previously reported, the total figures show 41 primary carcinomas of the hepatoma type and 14 of the cholangioma type. Mention has been made before of the frequent association of hepatic cirrhosis and primary hepatic carcinoma, and our findings confirm the fact that these two conditions occur together in almost every case.

As indicated in our previous report,¹ the Chinese whom we see have or have had a high incidence of infestation with intestinal parasites. The presence of these parasites may antedate by many years the development of liver disease. In our first series in none of the Chinese was the liver fluke, *Clonorchis sinensis*, demonstrated at the time of necropsy, but we presumed that such infestation might have led to a hepatitis, then a cirrhosis, and finally a primary carcinoma. In the present series the parasite was found in four Chinese at autopsy. The relation of the liver fluke to chronic liver disease including primary cancer would seem to merit consideration, though there is no evidence that among the whites intestinal parasites of any sort played any part in the etiology.

TABLE II
Incidence of Primary Carcinoma of the Liver
(Necropsy)

	No. of Cases	No. of Necropsy	Percentage Incidence
1920-1931			
White	2	1828	0.109%
Chinese	10	139	7.18%
Japanese	—	—	—
Total	12	1967	0.61%
1932-1944			
White	16	7340	0.26%
Chinese	25	446	5.44%
Japanese	2	—	—
Total	43	7786	1.81%
Grand total	55	9753	0.56%

The figures for incidence at necropsy of this form of malignant disease are shown in table 2. In our first report the incidence among whites was 0.1 per cent, which is about that usually reported. Among Chinese, however, the incidence was 7.1 per cent, which brought our total incidence to 0.6 per cent. In the present series of 43 cases the incidence at necropsy among whites has more than doubled to 0.26 per cent; the Chinese are not quite so high at 5.4 per cent, but the total incidence of 1.8 per cent is three times that in the earlier series. The incidence of primary carcinoma of the liver in all cases over the whole 25 year period is 0.56 per cent.

The average duration of the disease, as judged by the interval between the onset of symptoms and death, was comparatively brief; in fact, primary carcinoma of the liver is one of the most rapidly fatal of all malignant neoplasms. It matters little whether the tumor is a hepatoma or a cholangioma as far as prognosis is concerned, nor is the duration of the disease much different in the whites or Chinese. Because of the well-recognized stoicism of the Oriental there were not a few instances in which patients of this race walked into Hospital a few days before death from primary cancer of the liver. Although the duration of symptoms and signs was about the same in both races, the whites were usually bed patients for a longer period than the Chinese. The average age at death from hepatoma is 49.5 years for Orientals and 66.07 years for whites, whereas for cholangiomas it is 51.4 for the former, and 59.7 for the latter. The onset of hepatic malignant disease of both types occurs earlier in Chinese than in whites.

The symptoms of primary carcinoma of the liver are those of a rapidly progressive cirrhosis of the liver, coupled with the symptoms of malignancy, cachexia, weakness and weight loss. The whole picture of cirrhosis is foreshortened, and the portal obstruction leads to early ascites with resulting abdominal distention magnified by the associated and rapid weight loss. There were certain symptoms which distinguished this condition from cirrhosis; pain, for example, was a presenting complaint, being abdominal in 19 cases and thoracic in 11. Other common symptoms were anorexia in 15, weakness in 11, and dyspnea in eight cases. Less frequently noted were drowsiness, numbness of the feet, indigestion, constipation, nocturia and urinary retention, diarrhea and nausea.

The physical signs were of greater importance in diagnosis. The commonest sign was ascites, present in 31 cases, although some fluid in the abdomen was always found at necropsy. Hepatomegaly, which was noted in 22 cases, was the next most common physical sign. The liver is enlarged and fixed early in the disease, with the result that the right diaphragm is elevated and shows diminished respiratory movement. This diagnostic feature as determined by roentgen-ray has been of some value. Ankle edema occurred in 22, weight loss in 17, and jaundice in 10 cases. Other signs which were less frequently noted were splenomegaly, abdominal tenderness, emesis, fever, hemoptysis, hematemesis, melena, hematuria, clay-colored stools, and carcinoma cells in the ascitic fluid. In the diagnosis of primary carcinoma of the liver, a negative finding by roentgen-ray in a gastrointestinal series is of some value.

The average duration of illness has been mentioned previously. The manner in which the illness terminated is of interest. Twenty-five of the cases died a cachectic death outwardly similar to that of death due to extensive carcinomas of other systems. Very occasionally this was associated with some degree of myocardial failure, chronic nephritis, or early evidence of infection, i.e., pleural empyema or bronchopneumonia. Massive hemorrhage from a ruptured esophageal varix or an intraperitoneal hemorrhage

from an eroded vessel in the hepatic tumor nodules accounted for death in 14 instances, and an additional death was due to abdominal hemorrhage, following perforation of an omental artery by the trocar on attempting a paracentesis. One death was due to an overwhelming infection of the liver with formation of an hepatic abscess and a right-sided pleural empyema. Another death was the result of cerebral infarction subsequent to thrombosis of a cerebral artery. However, in both of these there was extensive malignant change in the liver, justifying their inclusion in this paper.

Although laboratory investigation has not been extensive, certain procedures were more or less routinely performed. The hemoglobin was invariably slightly lower in the Oriental than in the white man, but both exhibited a hypochromic normocytic anemia, and in those instances of massive hemorrhage a lower hemoglobin concentration was recorded, as would be expected. The white cell count was usually within normal limits; in those cases with a leukocytosis there was no change in the differential count. The sedimentation rate (modified Westergren) was elevated in every case in the manner which indicates existence of an active chronic disease. Examples of elevated non-protein nitrogen were quite rare. The Kahn reaction was negative.

On many occasions during the past there have been patients admitted to the Vancouver General Hospital for whom we have considered the possibility of a primary type of carcinoma of the liver in the preliminary differential diagnosis. In the light of further clinical and laboratory investigations, we have made this the final diagnosis with confidence in some of the cases here reported and had it confirmed at autopsy. There follows a presentation of two such cases, the first a male Oriental and the second a female Occidental.

CASE REPORTS

Case 1. E. F., male, aged 59, was admitted November 20, 1943 and died January 16, 1944. The admission complaint was moderately severe abdominal pain of three days' duration. This patient was not articulate. Through his friends, a history was obtained of intermittent attacks of epigastric and right upper quadrant pain which were of varying duration, over a period of nine months. These were not influenced by food. The attack which had precipitated this admission had begun with unusual suddenness and had rapidly reached a degree of severity which was difficult to bear. The pain was constant and was not confined to any particular quadrant. There was no associated nausea, emesis, diarrhea, or abdominal cramp. The signs and symptoms of shock were not present.

The history indicated that he had been seriously ill when a child in China, but since coming to Canada in 1912 had experienced no incapacitating illness.

Functionally, the man had no complaints referable to any of his systems, with the exception of a slight degree of dyspnea on exertion.

Physical investigation was negative until the abdomen was examined. This was protuberant and showed slight edema of the abdominal wall. This superficial edema involved the entire trunk, genitals and both inferior extremities. Palpation over the entire abdomen revealed no areas of tenderness, and there was no regional muscular rigidity. The right upper quadrant and epigastrium were occupied by a smooth, firm,

non-tender mass which moved slightly in the epigastric region during deep inspiration. Upon percussion of the right thorax, there was diminished pulmonary resonance, and the area of dullness was continuous with the mass discovered in the abdomen. Conclusive evidence of free peritoneal fluid could not be obtained, and there were no further abnormalities noted in the abdomen.

Radiological and fluoroscopic procedures indicated that the right leaf of the diaphragm was abnormally high and fixed in position. It was the radiologist's opinion that the distortion was due to subdiaphragmatic rather than pulmonary causes.

Laboratory procedures showed repeated urinalyses to be consistently normal. Hemoglobin was 70 per cent. The total red blood cell count was 3,600,000. Color index was 0.91, and the red blood cell morphology was regular. Initial white blood cell count was 17,600, with 60 per cent mature polymorphonuclears, 32 per cent immature polymorphonuclears, 5 per cent lymphocytes, and 3 per cent monocytes. The sedimentation rate was 20 mm. in 15 minutes and 81 mm. in 45 minutes (modified Westergren). Subsequent white blood cell counts showed a gradual descent to a value slightly higher than normal, with a corresponding decrease in percentage of immature polymorphonuclears. The blood Kahn reaction was negative.

The temperature on admission was 99.4° F., and the pulse rate was 94. During hospitalization the temperature fluctuated from normal to a high of 102° F., and the pulse rate from normal to 104 per minute. Although it became obvious that the patient was gradually deteriorating, he only occasionally complained of high abdominal discomfort. A diagnosis of primary carcinoma of the liver was recorded.

The necropsy findings were: hepatoma type of carcinoma of the liver, hepatic cirrhosis, bilateral pulmonary congestion and edema, bronchopneumonia, myocardial degeneration, chronic passive congestion of the spleen and kidneys.

The second illustrative case is more interesting since the problem of diagnosis was complicated by the fact that primary carcinoma had never been seen previously in a woman patient. A tentative antemortem diagnosis of primary carcinoma of the liver was recorded but was never seriously considered.

Case 2. M. H., female, aged 51, was admitted October 23, 1944 and died December 7, 1944.

The patient was essentially well until three days prior to admission. There was at that time a rather sudden onset of moderately severe pain originating along the anterior and lateral aspects of the right rib margin. This later radiated at intervals through the chest to the back up to the region of the right shoulder. The pain was constant in character and aggravated by inspiration but not in a knife-like manner. The discomfort was not favorably influenced by light breathing or the adoption of different postures. The patient gave no sign of gastrointestinal disease of any kind prior to or during the illness. The past history was non-contributory. At the time of the first physical examination there was a questionable slight icteroid tinge to the sclerae. On auscultation of the lungs no adventitious sounds could be heard and the right base posteriorly was negative. The blood pressure was 150 mm. Hg systolic and 90 mm. diastolic. On abdominal examination only a slight degree of right upper quadrant tenderness could be found.

The temperature on admission was 102° F.; pulse rate was 80 per minute; and respirations were 20 per minute. The clinical impression was: (1) subdiaphragmatic abscess, and (2) diaphragmatic pleurisy.

Roentgenogram of the chest showed both elevation and fixation of the right diaphragm with slight signs of pleural thickening. There was no indication of active pulmonary disease. At this time the roentgen-ray diagnosis was costophrenic pleurisy, though a second radiological opinion was that the changes could be due to increased abdominal pressure.

Examinations of the blood and urine were essentially negative. The van den Bergh reaction was within normal limits.

During subsequent days the temperature showed a diurnal variation from 99° to 103° F., and diaphoresis was constantly marked. Strapping with adhesive tape, local heat, sulfathiazole, penicillin and codeine did not benefit the thoracic distress or the fever. A second roentgenogram was similar to the first, but the interpretation was that a subdiaphragmatic abscess might be present. At about this time the white blood cell count was 13,300 with 40 per cent matured polymorphonuclears, 28 per cent immature polymorphonuclears, 27 per cent lymphocytes, 3 per cent monocytes and 2 per cent eosinophiles. The hemoglobin was 72 per cent, red blood cell count 3,800,000, and color index 0.94. One month following admission and following consultation with a surgeon resection of a right rib was carried out with the intention of exploring the right subdiaphragmatic space. Upon viewing the diaphragm the surgeon noted tumor nodules and the operation was terminated.

At no time during the illness did the patient feel well. Deterioration was slow but steady. Pain was constant, gradually becoming localized over the right lower chest and right upper quadrant. At the end of the second week, one of us (J. G. M.) felt a nodular, firm, slightly tender mass in the right upper quadrant and assumed it to be the liver associated with malignant involvement. The operation, of course, had produced no benefit.

At autopsy there was found primary carcinoma of the liver of the hepatoma type with extensive metastases to the periaortic lymph nodes and the nodes of the sigmoid and rectal mesentery. There was also a rather large tumor mass adjacent to the rectum. This had perforated into the rectum but had apparently produced no sign or symptom. The liver weighed 3840 grams and contained an enormous tumor growth, measuring 15 cm. in diameter in the right lobe. Numerous other nodules were scattered throughout the hepatic parenchyma. Cirrhosis was not marked.

Had these findings occurred in a man and particularly in a Chinese, the preliminary diagnosis of primary carcinoma would have been made because of the persisting right upper abdominal pain and high fixed diaphragm and diaphoresis in a patient who presented no pulmonary or pleural infection and in whom there was no intra-abdominal lesion likely to cause a subdiaphragmatic abscess.

PATHOLOGY

Primary carcinoma of the liver presents itself in two forms: the hepatoma type, arising from liver cells; the cholangioma type, arising from bile duct epithelium. There appears to be much greater pleomorphism and polymorphism of the cells in the former type with a fair number of tumor giant cells present in many of the cases in this series.

The major distinction in the two types is the abortive attempt at bile duct formation and the relatively smaller size of the tumor cells in general in the cholangioma type. The gross tumor masses in the liver are generally bulkier in the hepatoma type.

There appears to be little question as to the relationship of cirrhosis to primary cancer of the liver, and a number of observers, chiefly Counsellor and McIndoe,² question the authenticity of a diagnosis of primary cancer of the liver in the absence of cirrhosis. It is interesting to note that in 87.2 per cent of the 55 cases here presented, cirrhosis was present. In the hepatoma type it was present in 96 per cent of the Orientals and 79 per cent of the whites, whereas in the cholangioma type it was present in 88 per cent of the Orientals and in 100 per cent of the whites.

In a previous paper¹ we stressed the possible association of liver fluke infestation with subsequent cirrhosis as precursors of primary cancer of the liver, as practically all of the Chinese residents in Vancouver are emigrants from the Kwantung province of China where fluke infestation (*Clonorchis sinensis* type) is said to be practically universal, and primary cancer and cirrhosis of the liver are common. In four cases of this series the *Clonorchis sinensis* were present. These facts, we believe, are more than coincidental. However, there is still the fact that, except for one of the white patients who had lived in India for a considerable number of years, all had been lifetime residents of North America with no suspicion of any liver fluke infestation.

It was also suggested in the earlier paper¹ that metastases occurred almost entirely via the blood stream but, in view of the fairly frequent secondary involvement of the perigastric, preaortic, retroperitoneal, mediastinal, peribronchial and, in one instance each, the inguinal and cervical lymph nodes, this must be amended to read: "That, while metastases are chiefly hematogenous, they may also be lymphogenous in origin" (table 3).

TABLE III

No metastases	32
Lungs	16
Perigastric lymph nodes	7
Pre-aortic and retroperitoneal lymph nodes	6
Mediastinal and peribronchial lymph nodes	4
Inguinal	1
Cervical	1
Vertebrae	3
Adrenals	3
Ribs	2
Spleen	2
Brain	1
Kidney	1

Secondary deposits originating from the hepatic carcinoma were found grossly in 18 different sites. However, on the whole, liver carcinoma are quite localized, with hepatomas somewhat more than twice as invasive as cholangiomas. By far the most common sites of metastases were the perigastric lymph nodes and the lungs, and it must be pointed out that demonstrable metastases must be considered infrequent and can only rarely be used as an aid to diagnosis, i.e., by biopsy. In all of our 55 cases, a sentinel node was recorded only in one instance.

The weights of the livers in this series were much lower than those recorded in the textbooks on medicine and pathology. The average for hepatomas was 2,695 grams, with a range from 890 grams to 6,650 grams. The average weight for cholangiomas was 2,808 grams, with a range from 1,020 grams to 5,800 grams. There was little real difference between the weights of each type in males and females.

One rather interesting feature of this series is the fact that in 32 cases no metastases were found, which is most unusual in view of the marked

tendency of the tumor tissue to involve the rich vascular bed in the liver substance.

CONCLUSIONS

There is presented a brief analysis of 55 cases of primary carcinoma of the liver found during a 25 year period.

The clinical symptoms and signs are described and the pathologic findings noted.

Whereas it was once true that primary carcinoma of the liver could only be diagnosed at autopsy, it is now possible to make such an antemortem diagnosis with reasonable accuracy.

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THE EFFECT ON THE PRECORDIAL ELECTRO-CARDIOGRAM OF INSULATING AREAS OF THE ANTERIOR CHEST WALL *

By ALBERT H. DOUGLAS, M.D., F.A.C.P., *Jamaica, N. Y.*, and
JERALD S. KALTER, M.D., *New York, N. Y.*

THE precordial leads have justifiably gained increasing importance in the past decade and considerable knowledge has accumulated concerning the significance of the various deflections in the standard positions. These leads are now used routinely to supplement the information given by the limb leads and, more particularly, to aid in the localization of myocardial infarcts, bundle branch block, and pathologic processes involving primarily the right or the left side of the heart. The localizing value of precordial leads results from the well known fact¹ that an exploring electrode on the

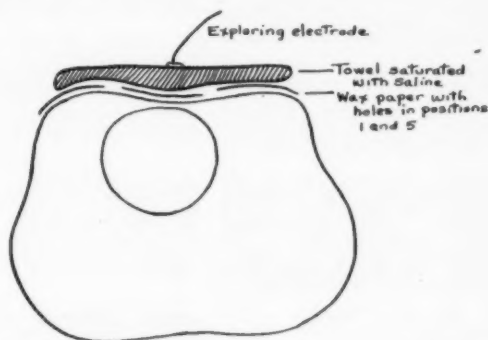


FIG. 1. Method of insulating anterior chest wall. The wet towel is in direct contact with the chest wall in the 1 and 5 positions only.

anterior chest wall produces an electrocardiogram which resembles that of the underlying epicardium and which is influenced most by the myocardium in proximity with the electrode. Thus, positions 1 and 2 on the anterior chest wall are used as indices of changes in the right side of the heart, and positions 5 and 6 are similarly used as indices of changes in the left side. The intermediate positions 3 and 4 are likely to be influenced by electrical changes from right or left and one must determine the direction of this

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From the Heart Station at the U. S. Naval Hospital, St. Albans, N. Y.

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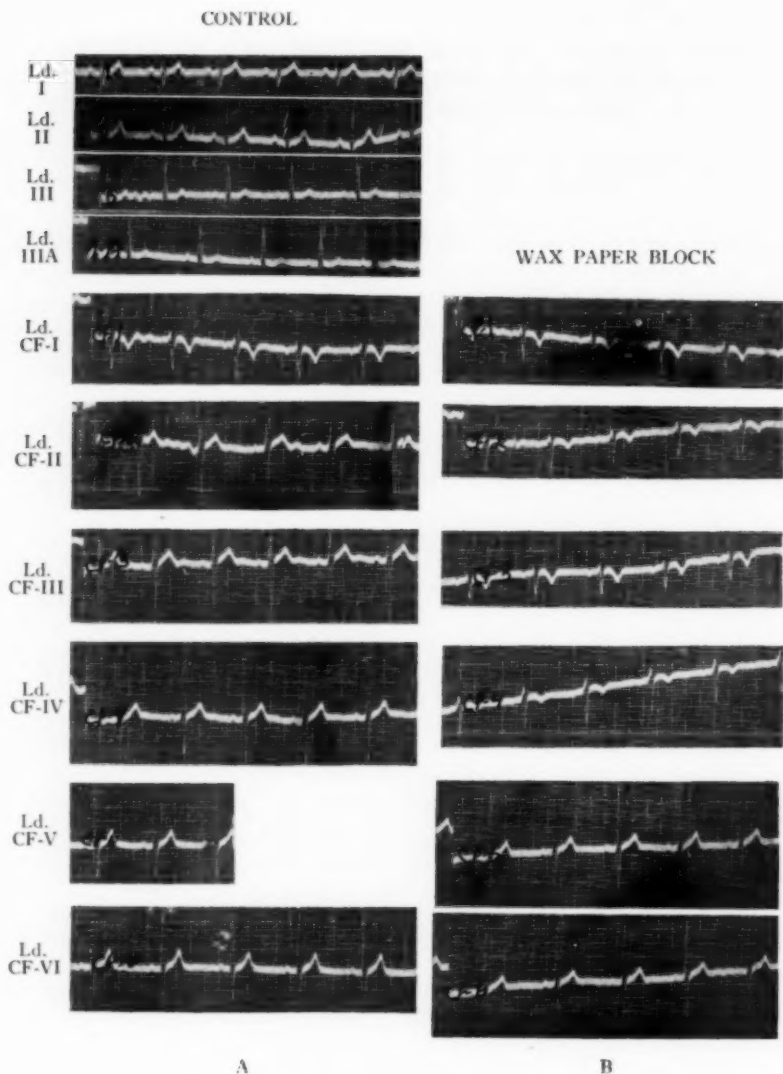


FIG. 2. *A. Control:* A patient with no evidence of physical disease showing inverted T-wave in CF_1 and upright T-waves in the remainder of the precordial leads. *B. Wax paper block:* T-wave is now inverted in CF_1 , CF_2 , CF_3 and CF_4 .

CONTROL

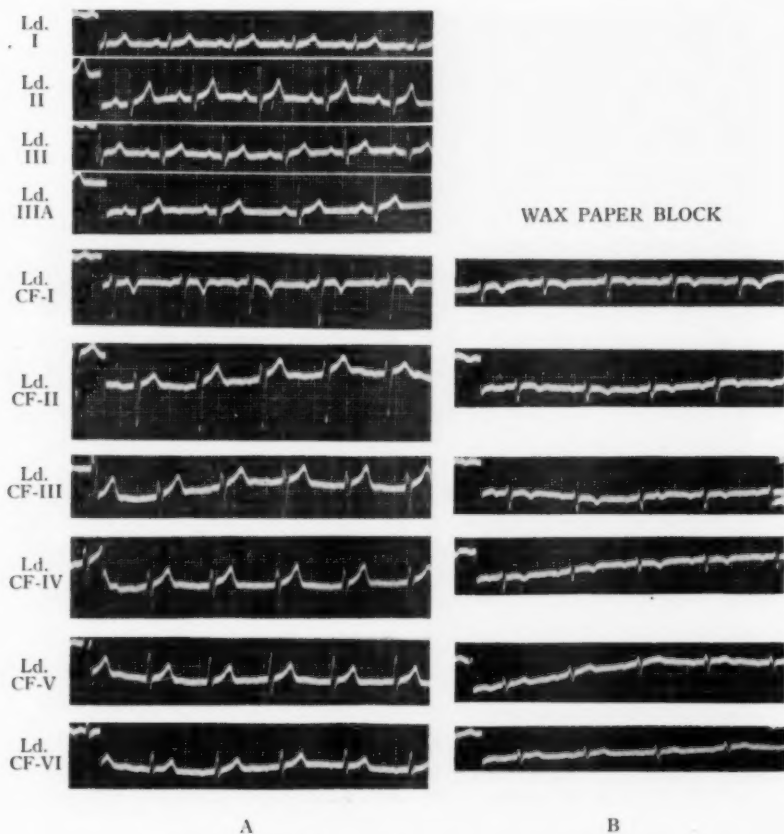


FIG. 3. Exemplifies same changes as seen in figure 2.

influence by comparison of these leads with the curves found in the other positions. If T-wave inversion in CF₄, for example, is associated with inversion in CF₅ and CF₆ while T tends to become increasingly upright in CF₃, CF₂ and CF₁, the effect is left sided. A right sided effect would, in reverse fashion, produce inversion of T in CF₁, CF₂ and possibly CF₃, with return to an upright direction in the CF₄ and CF₅ positions. It is evident that, if one takes just CF₄, it is impossible to decide from this precordial lead alone whether changes are the result of damage to the right or to the left. In general, when five precordial leads are taken, one can by comparison localize with accuracy. At times, however, such interpretation is rendered

CONTROL

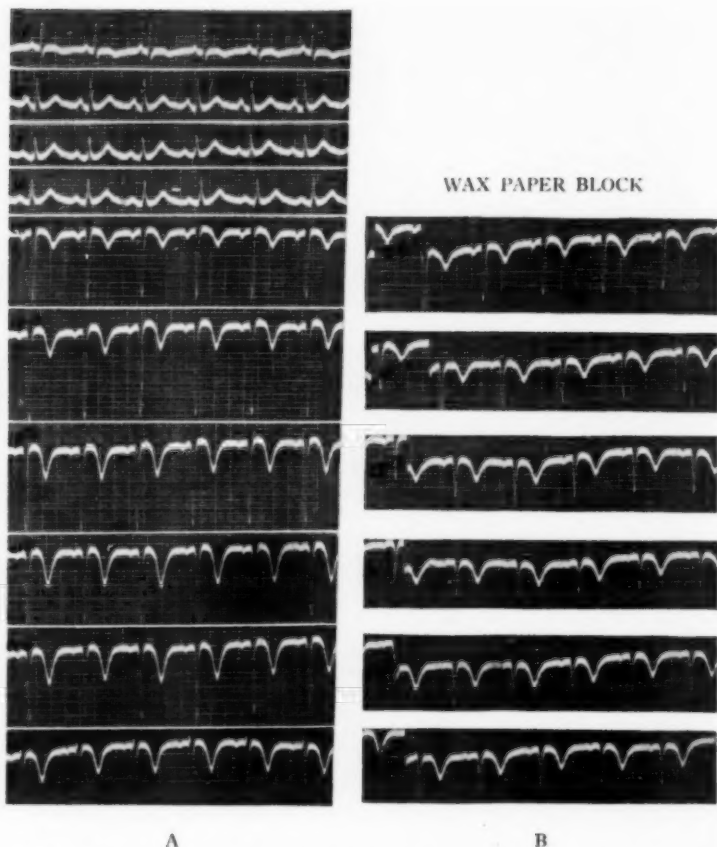


FIG. 4. *A. Control:* Case of anterior myocardial infarction with inverted T-waves and an absent R deflection in CF_1 through CF_6 . *B. Wax paper block:* Changes similar to the control still present in the intermediate positions despite the block.

difficult or inaccurate by neutralizing effects produced on the exploring electrode in a particular position by cardiac zones that are relatively remote. In this study we have attempted to analyze such effects of remote cardiac zones in an effort to determine their relative importance and the degree to which they may distort the electrocardiographic picture contributed by the cardiac zone nearest a particular chest wall position.

Method: We used wax paper on the anterior chest wall to insulate positions other than those studied. In this study we limited ourselves to in-

vestigation of the cardiac zones primarily responsible for the CF_1 and CF_5 patterns. Holes an inch in diameter, the size of the exploring electrode, were cut in the paper in the 1 and 5 positions. A towel saturated in warm saline was then placed over the wax paper and the exploring electrode was placed in succession in positions 1 to 6 on top of the wet towel. This series of electrocardiograms was compared with control tracings taken in the usual manner prior to the application of the wax paper and towelling. Figure 1 illustrates the method used. In addition to the precordial leads the three limb leads were routinely taken and also Lead III with the patient in deep inspiration, designated as 3A.

Results: Twenty-five subjects were studied in the manner described, including normal controls, and patients with myocardial infarction, bundle

CONTROL

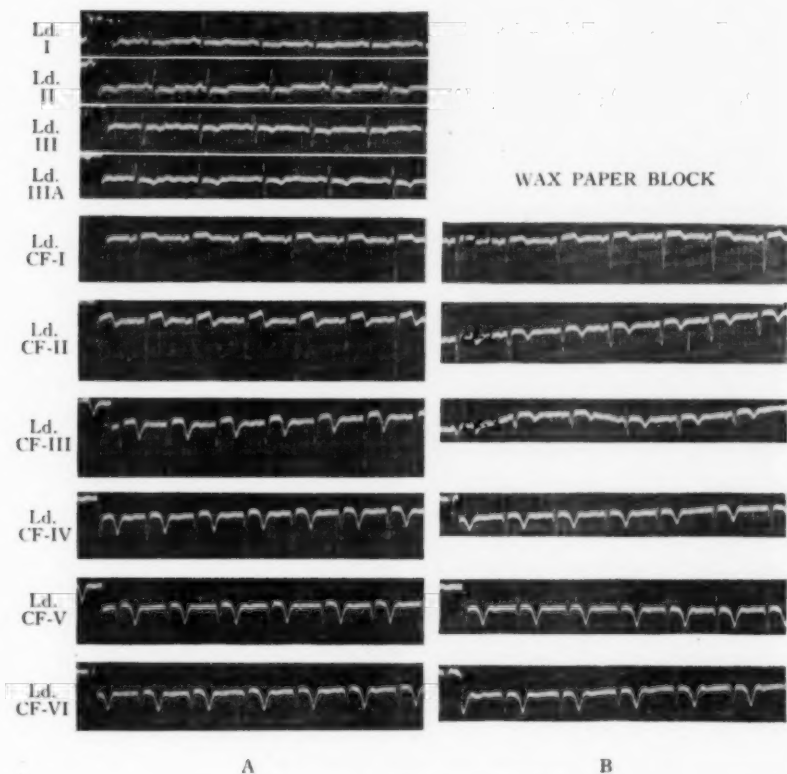
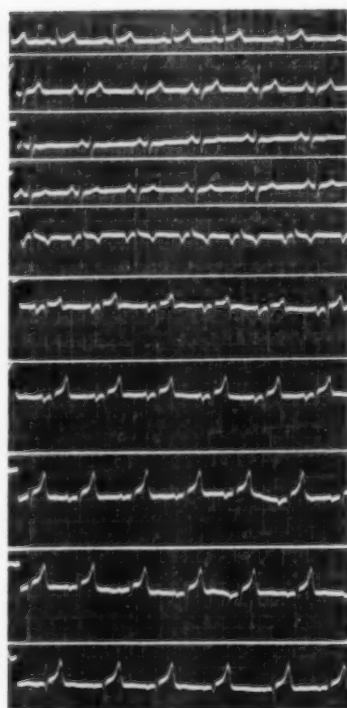


FIG. 5. Exemplifies same changes seen in figure 4.

branch block, and patterns of left and right ventricular strain. Several typical experiments are shown in figures 2 to 9.

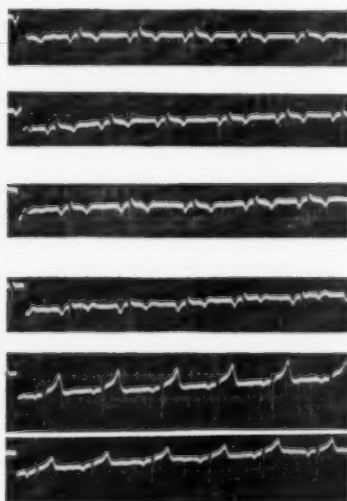
A comparison of the two sets of precordial electrocardiograms in figure 2, taken from a normal individual, shows that the insulation of the intermediate positions has caused the CF_1 pattern to be carried to the left as far as CF_4 . In figure 3, another normal, one finds differences in all the leads and it is of interest to observe that the QRS pattern is altered as well as that of the T-wave. Again T-wave inversion in the experimental tracings is found as far to the left as CF_4 . In figure 4, taken from a patient with anterior myocardial infarction, little difference is seen in the two sets of curves except that the small R found in CF_6 does not appear in the second

CONTROL



A

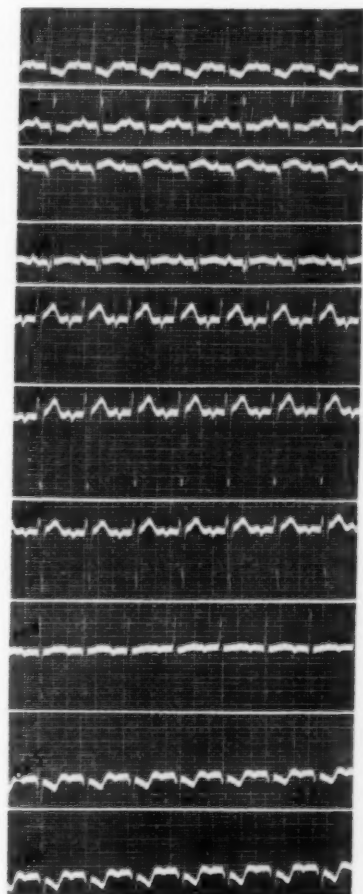
WAX PAPER BLOCK



B

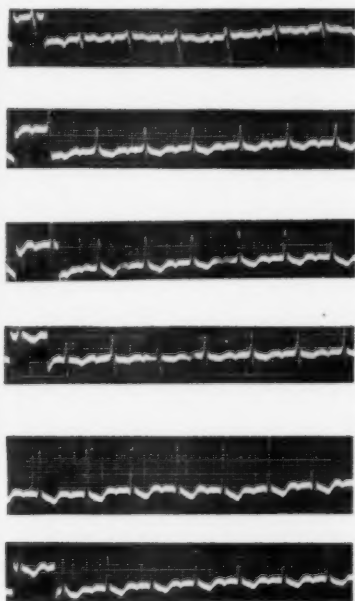
FIG. 6. *A*, Control: Case of old antero-septal myocardial infarction where the T-wave is inverted in CF_1 but upright in the remainder of the precordial leads. *B*, Wax paper block: T-wave is now inverted in CF_1 , CF_2 , CF_3 and CF_4 .

CONTROL



A

WAX PAPER BLOCK

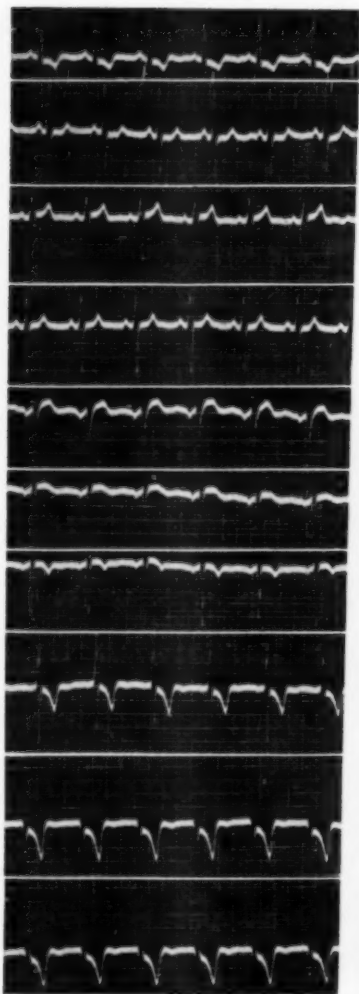


B

FIG. 7. *A. Control:* Case of left heart strain with inversion of the T-wave in CF_3 and CF_6 .
B. Wax paper block: T-wave is now inverted in CF_2 , CF_3 , CF_4 , CF_5 and CF_6 .

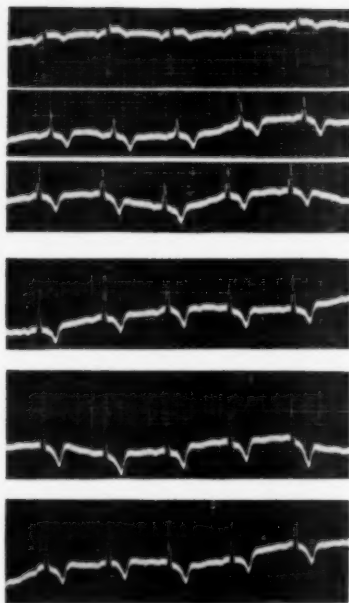
series, this position having been insulated. Figure 5 resembles the previous illustration. Here, however, the experimental curves show an R-wave in the 4 and 5 positions not found in the first series, where a notch on the descending limb of QS appears instead. This difference is probably due to the influences of cardiac zones in proximity with positions 2, 3 and 4 which

CONTROL



A

WAX PAPER BLOCK



B

FIG. 8. *A. Control:* Case of left heart strain showing embryonic R-wave in CF_1 , CF_2 , and CF_3 with a prominent R-wave in CF_4 , CF_5 and CF_6 . *B. Wax paper block:* Prominent R-wave is now present in CF_2 , CF_3 , CF_4 , CF_5 and CF_6 .

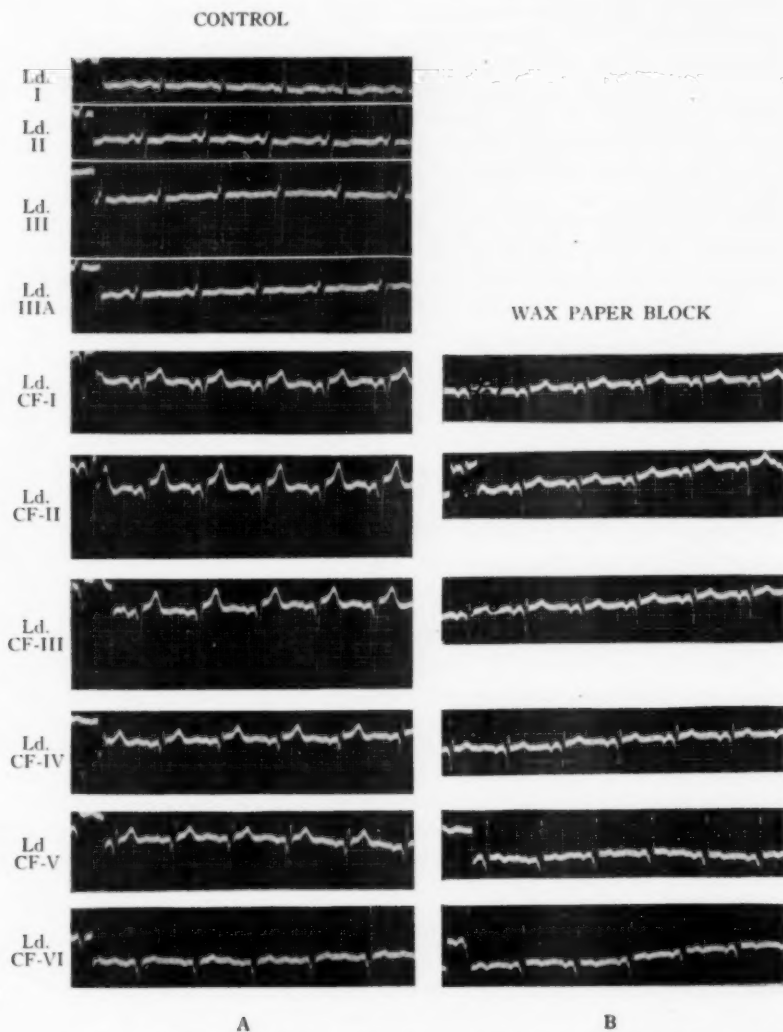


FIG. 9. *A. Control:* Case of marked hypertension with history of a previous myocardial infarction where the T-wave was diphasic in Lead I but upright in CF_1 and CF_2 . *B. Wax paper block:* T-wave in CF_1 and CF_2 is now inverted.

have been blocked by the wax paper. Figure 6, taken from a case of old antero-septal infarction, shows a change from an upright to an inverted T in positions 1 to 4, and, also; a reduction in the height of R in CF_6 —this effect, therefore, is contributed primarily by the CF_6 position which has been blocked. In figure 7, taken from a patient with left heart strain, one finds inversion of T, originally limited to CF_5 and CF_6 , in all positions except CF_1 ; and positions CF_3 and CF_2 show taller R-waves—the blocked positions, therefore, have contributed deep S and positive T components. Figure 8 resembles figure 7. In this case, too, the blocked intermediate positions are shown to have contributed a negative component to the QRS and a positive component to the T-wave of the standard precordial tracings.

Figure 9, taken from a patient with marked hypertension and old anterior wall infarction, is of interest because of the appearance of a diphasic T in the 5 position and an inverted T in the 6 position, not found in the control series. Apparently, positive components contributed by positions 4, 3 and 2 have obscured T-wave inversion which became manifest only after the intermediate positions were blocked. Lead I shows inversion of T and more nearly resembles CF_5 and CF_6 of the experimental series than it does the standard curves. The similarity between Lead I and Lead CF_5 is well known. At times, however, as in the case at hand, differences appear in these leads which can be clarified in the manner indicated.

DISCUSSION

The findings reported emphasize the fact demonstrated so well by Wilson and his colleagues¹ that the precordial electrocardiogram is a composite in which the cardiac zone nearest the exploring electrode dominates the picture. However, the effects of more remote zones cannot be disregarded and the proper evaluation of any one precordial lead requires careful comparison with the others. In general, the influence of cardiac zones not in proximity with the exploring electrode has been neglected in the literature. We believe that this influence is frequently greater than has been generally appreciated and that it can be made more evident by the insulation of areas of the anterior chest wall. By this method we have attempted to distinguish QRST changes produced by the myocardium in proximity with the exploring electrode from those contributed by zones further to the right or left; and also to throw light on some apparent discrepancies between Leads I and CF_5 which usually are much alike.

When the heart muscle nearest a given chest lead produces a negative deflection and adjacent zones produce positive deflections the actual curve written may be a resultant of opposite effects. On the other hand, the underlying myocardium and adjacent zones may both contribute components in the same direction with an addition of effects. For example, *low* upright T-waves in CF_4 and CF_5 associated with *tall* upright T-waves in positions to the right may be just as good evidence of left ventricular strain as in-

version of T in CF_4 and CF_5 when T-waves to the right are low or inverted. It appears evident that one cannot interpret accurately the significance of the height and direction of any deflection in a precordial lead without determining its relation to comparable deflections in other areas.

A related problem concerns certain differences between Leads I and CF_5 that occasionally appear, particularly in the direction of the T deflection. The fact that these leads usually present similar curves is well known. As illustrated in figure 9, T-wave inversion may at times be found in Lead I but not in CF_5 because T-wave positivity contributed by zones to the right obscures the change in the chest lead. The inversion, however, becomes apparent when the interfering zones are insulated in the manner described.

CONCLUSIONS

1. The insulation of certain areas of the anterior chest wall enables one to distinguish the electrical effects contributed by the myocardium nearest a particular chest wall position from those contributed by zones that are more remote.

2. The effects of remote zones are frequently greater than is generally appreciated.

3. These effects must be taken into account when precordial electrocardiograms are interpreted. Accurate analysis of the electrocardiographic picture in a particular precordial lead is impossible without careful comparison with the picture in adjacent leads.

4. Some apparent discrepancies between Leads I and CF_5 are explained by the technic described. They result from the interference of relatively remote cardiac zones with the CF_5 pattern.

The authors wish to express their appreciation to Chief Pharmacist's Mate E. D. Schwartz, USN, for his excellent technical assistance.

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THE GOLDEN GATE OF MEDICINE*

By ALAN GREGG, M.D., *New York, N. Y.*

MAY I begin with the bold hope that the almost effortless mastery of time and space which has brought you here has not imposed sophistication as the price of comfortable travel, nor robbed you of a pilgrim's vivid sensitiveness to stark and simple things. Unless, for a moment at least, you can give yourself to the realization of what this city of San Francisco has been and will always be, you will miss the significance as well as the fun of these meetings. That is why I hope you will abandon yourselves to the simplest things, dispense with all your reservations except perhaps the Pullman variety, and treat yourselves here to that rarest of American luxuries, contemplative reverie.

As one stares into a hearth fire the better to ruminate and reflect, let us think for a moment on the meaning of the Golden Gate. It made this city of San Francisco the goal of many an overland traveler and yet later a point of departure par excellence for those whose restless energies were not exhausted by the crossing of a continent. Fabulous as journey's end for the covered wagon, the Golden Gate redoubles its charm by being at the same time the gateway to the incredible variety of the Pacific Ocean. It was the spot where prairie schooners offloaded their tireless crews to real schooners and the Far West turned to the Far East in the paradox of the circle.

I hold to that word variety—the *variety* of the Pacific Ocean. For most of us have reached here the end of a known experience and find ourselves on the edge of a still greater ignorance. So I would find it simple and appropriate here at the Golden Gate to ask the question, "What next in Medicine?" It is a fitting time to look back over the road by which we have come, and forward to new ways of travel and new experiences. Because of the very simplicity of the comparison I want to talk about the Golden Gate of Medicine, for in so many ways in Medicine we seem to be at the end of one road and restlessly realizing it. Before we ask, "What next?," let us look back.

The past 75 years in medicine—our generation and that of our teachers—seem to me to have been influenced by an idea so general and pervasive that it escaped explicit attention. At the same time it has been so rewarding that, even unrecognized, it has dominated our activities. Even now it may seem elusive, for like magnetic attraction its effects are more easily pointed out than the force itself. This idea, or prevailing assumption, concerned not the description nor the treatment of disease, but its causation. This powerful idea involved the conviction, or at least the rapidly spreading

* Convocation address at the Twenty-ninth Annual Session of the American College of Physicians, San Francisco, California, April 21, 1948.

assumption, that each disease has its own specific, single and sufficient cause. We cannot realize what a radical release this idea brought from the multiple yet simultaneous complexities of medieval thought—the tradition of the astrologers so nicely preserved for us in the very word *consider*, *-sidera*, the stars, and *con*, taken together.

In earlier centuries there had been speculation a-plenty. There had been descriptions of disease that cannot be improved upon today. There had been scattered fortuitous discoveries of remedies and effective methods of treatment. Then there gradually came a new approach. There is no particular year when such an assumption can be shown to have begun, nor any one event as its point of origin. But the discoveries of Pasteur and those that satisfied Koch's postulates, gave unexpected and yet convincing evidence that many diseases actually had specific causative agents. The immense success of these discoveries went further and focused most of the minds of the generation preceding ours on the problems of the cause of disease, and even quickened the suggestion that every disease must have its one unique, and uniformly effective cause. Now an idea that is both simple and immensely rewarding is certain to obtain increasing credence and eventual acceptance. Surely the concept of direct and unique causation is simple—indeed has proved deceptively simple. And yet what a harvest it reaped! Anthrax, hydrophobia, surgical sepsis, typhoid, diphtheria, tuberculosis, cholera, dysentery, childbed fever, tetanus, syphilis—what triumphs for almost a single generation! In the face of such a record it seems almost churlish to point out that this successful and all-pervading preoccupation with the specific causation of disease has produced anything in addition to the long desired mastery of many terrifying afflictions of mankind.

But the results have been more far-reaching than we realize. There has been a cataract of consequences, intellectual, ethical, social, economic, and educational, deriving from the effects of this idea that every disease has its own single and sufficient cause. Like a sudden and far-flung military advance it has called for extensive rearrangements along the entire line and in the services of supply. What are these changes?

First, by so much as you discover the causes of various diseases you begin the control of their incidence. Rationally and effectively to prevent disease was something startlingly new. The occurrence of disease had been for two thousand years considered a matter of chance or fate. We still exemplify that attitude when we say, "fortunately I have enjoyed good health all my life," but that phrase is more untrue now than we realize, for the diminished incidence of many a disease is now no longer a matter of luck but the result of the use of intelligence and effort and money. Epidemics that used to be excused as acts of God are now not excused as the results of the inactivity of man. In short, the incidence of many diseases has been moved from the area of chance to the area of choice. That is a vast change intellectually. Not only intellectually but also morally, for such a series of ac-

complishments leaves us with a new system of ethics to devise, somewhat as the perfection of the automobile has called for new traffic laws. As physicians we cannot evade a moral responsibility that goes with our newly acquired power. Having learned how disease comes about we find ourselves answerable for why it should occur at all. The oath of Hippocrates makes no reference to the physician's duty to prevent disease though we still solemnly intone it to graduating students as an admirable credo of our profession. Admirable but no longer adequate. No less paradoxically, the layman demands from us protection and prevention, but still is loath to pay for it because health still seems to him a matter of luck—and by definition nobody ever pays for good luck. So there are economic and social consequences as well as ethical. For mark you, the general public is beginning to realize that the well-trained doctor and his helpers can now deliver much that is as essential to life and comfort as food, clothing, and housing. But until people clearly and fully see that prevention and good care are as reasonable an expense of living as any other essential, we doctors shall drag on in the confusion of their thriftlessness, a confusion embittered by charges and countercharges of exploitation and evasiveness, of extortionate doctors' charges and patients' improvidence. The mastery of the specific causes of so many diseases has whetted the public's appetite for more. Our generation happens to live at a time when the cost of keeping well or getting well is increasing. The laity is only beginning a great transition from the easy indolence of regarding health as good luck, to the sterner realization that like food and housing, health can be had and must be budgeted and paid for.

One further fact will be recognized but only with harrowing delay; namely that the cost of training good doctors must be regarded as part of the cost of medical care, and like other forms of public education, is a reasonable and indeed a desirable charge upon the people's capacity to earn. Speaking of the people's capacity to earn, Americans spent for beer, wine and whiskey in 1946 eight billion seven hundred million dollars. I cannot escape the rueful reflection that we are just pikers when it comes to paying for medical care; perhaps the vulgar fact is that an alcoholic sense of well-being outbids being well. And I ought to add in justice to our Californian hosts that not all that eight billion seven hundred million was consumed in solitary drinking. Would that medical care had more of the exhilaration of conviviality! Perhaps the gregarious uproar of a medical congress dedicated to reducing illness is a sage substitute for the excitement of the alcoholic illusion of well-being.

The constant interest in causation that has prevailed during the past 75 years has produced another important effect. Scientific medicine is essentially an affair of the intellect. Consequently the attitude of two generations preoccupied with the cause of disease has been to regard the patient as presenting an intellectual puzzle. Let me repeat that this attitude was in many ways an immeasurable improvement upon the fumbling and bewildered empiricism of an earlier day. But to regard a malady as an intellectual

puzzle, provides the physician with such an absorbing task that he commits the commonest error of the scientific mind; he forgets, or overlooks, or ignores some important variables in the equation he is attempting to solve. Fascinated by formulations of disease which took beautifully precise account of the factors of bacteriology, immunology, cellular pathology, biochemistry, biophysics, and physiology, the clinician of the past two generations has taken at times too little account of the psychological factors—the patient as a person, the emotional aspects of his disorder, and the disorder of his emotions. Only because the pathological and physiological factors were so complicated, and yet so beautifully verifiable, did the clinician's attention often become almost blind to the psychological factors. Now a sleight of hand artist can divert our attention from one move he makes by making at the same instant another move that is spectacular and preoccupying. "Look at the dicky bird!" is in effect a blinding command. The astute boxer feints with his left to afford his right hand a mellow target. Of course Nature seldom feints deliberately to divert our attention. But, science provides us with instruments of entrancing accuracy, with oil-immersion lenses and potentiometers and spectrographs and x-rays, all of which are superbly efficient for seeing parts of the total picture. But even these remarkable instruments do not excuse us from the task of looking at the whole picture, or of deciding what part of the total picture is worth looking at. Quite to the contrary they make it seductively easy to look at something merely because it can be seen. Now even if an instrument of precision will automatically register, measure, and record a singularly active and colorful dicky bird, we may be giving all our attention to what is no better than a dicky bird for all its beautiful verifiability. If I may offer a facetious suggestion—why not add one more word to our medical dictionaries—*ornithographs*, a collective term to describe all the pictures of the dicky birds that deflect our attention from what is important, by substituting mere precision for true comprehensiveness of observation? Rapt attention to the part is the best guarantee that the whole will be ignored. Of course when the part explains the whole, attention to it is an elegant procedure, but when the part obscures the whole, preoccupation with the part exemplifies misleading exactitude, and science at its worst.

If the search for the direct and single and ultimate causes of disease is going to continue to be the characteristic and dominating preoccupation of medicine for the next two generations, then I would expect that over the same interval there will be a continuing neglect of chronic disease, of rehabilitation therapy, of the care of the patient as a person, of the psychological counterparts of disease, and of the art of medical education. Any of these aspects of medicine will be neglected where causes preoccupy the doctor's attention. And I would not be surprised at the restlessness of patients at being considered mere intellectual puzzles; nor at their nostalgic references to the old-style doctor who knew his patients (and, we may add, knew his patients better than he knew their organic diseases); nor at the growing

popularity of the nursing profession which is pre-occupied with treatment, not causes; nor at the acceptability of osteopaths and chiropractors who all but dispense with the problem of causation, and thus get down to the business of treatment with noticeable dispatch.

But of all the aspects of medicine which have been eclipsed by the absorbing and rewarding preoccupation of seeking the causes of diseases, the most elusive and most important of all is medical education; the educational aspect of medicine; the fact that medical education is not to be left as a random and casual set of initiatory rites and vigils for apprentices, but is a form of education and a most important form too. In the excitement of a flood of scientific discoveries we have ignored the truth that medical teachers have duties purely as teachers. We have acted as though a brilliant teacher had little to offer to the progress of medicine. We have ignored the fact that medical schools belong to still larger and more significant things called universities; that medical schools have problems as all schools have problems; and obligations as all schools have obligations. And we have almost forgotten that the deans should know, and care, as much about the technics and problems of teaching as the deans of other faculties.

There is not time to expand and explain in full each of these consequences, intellectual, ethical, economic, social and educational that derive from the preoccupation of medicine with the idea of causation. But the thesis that the dominating and most pervasive characteristic of medicine over these last 75 years has been this preoccupation with the cause of disease, explains and illuminates more of our past successes and more of our failures, more of our present strength and more of our current problems, than any other interpretation of our relatively recent past.

If this thesis be sound, then we can also understand why some of the efforts in the past four decades seemed, when they appeared, to be so new and interesting. We can see why these novel movements seemed to be refreshing statements of ignored or neglected fact, perhaps at variance to the preoccupation with cause, or at least complementary to it, and sometimes even challenging its dominance in medicine. Let me mention a few. Richard Cabot's espousal and development of Medical Social Service. Abraham Flexner's insistence that medical education must be dealt with as a form of education. The Commonwealth Fund's support of Child Guidance. Clifford Beer's creation of the Mental Hygiene Movement. Kretschmer, Pende and Draper as protagonists of Constitutional Medicine. Sir Thomas Lewis' championship of the importance of the natural history of disease. Francis Peabody's book on the "Care of the Patient." Canby Robinson's book, "The Patient as a Person." Howard Rusk's remarkable work in the field of rehabilitation medicine. And some more general trends: the steady rise of Public Health and Preventive Medicine, the unexpected development of Psychiatry, the establishment of a chair of Social Medicine at Oxford, the Goodenough report that recommends a reform of medical education in Great Britain in the direction of a larger emphasis on preventive medicine and

psychiatry; the report of the Committee on the Cost of Medical Care; and the current discussions of the distribution of medical care.

All these phenomena, it seems to me, are related and understandable, when we realize that the knowledge of cause has given our profession a measure of control over disease, which forces upon us new ethical standards, a new social status, and also reform in medical education, including the obligation to realize that we must reckon with more than single and unique causation when a patient comes to us. We have come to see that we must add more factors to our equations of illness—the factors, for example of emotion, or of heredity or of social and economic status of the patient. We must teach these factors, not tacitly admit them. We must further expand our thinking from simple and unique causation to include a knowledge of the laws of pure chance, of multiple causation and correlations.

I trust this does not seem too abstract and inapplicable to the present tasks that face American medicine, for if we are now at the Golden Gate and outward bound there are more urgent issues to deal with than a mere rationalization of our experience to date. They may not be as clear as the lessons of the past but they are new and pressing.

Among the present practical problems which affect, and might well concern the American College of Physicians, is a development of relatively recent years, the certification of specialists. If only to encourage discussion upon that theme, I will offer some critical comment from the viewpoint of one who believes in the rule that intense attention to one thing almost guarantees the neglect of another. It has been somewhat sarcastically observed that military staff-officers prepare for the next war by learning how to fight the last war better. If we devote the present vast energy and attention to raising the standard of performance in the application of what is already known, will American medicine be as alert and adaptable to change as it wisely should? In a world where in some ways change is the only constant, can we be wise to devote our attention away from the ability to change? Are we prepared to believe that nipping the laggards is the essence of leadership, or that enforcing minimal standards will ever discover or encourage originality and advance?

For a specialty to attempt to improve the performance of its members and give a better significance to its status, is admirable. But there is an implication in the method used that is not admirable. It is misleading and dangerous. The implication is that if any group of specialists decide to clean house and criticize themselves they should be given carte blanche and let alone. That is as false as to say that if you are virtuous according to your lights you are therefore moral, or that if each nation follows the dictates of its own conscience the result will be acceptable to all the others. For the fact is that if, after you have finished your own house cleaning, the neighbors still complain, then you may not be through after all. It seems important then to assert at the outset, that although a specialist society should be the first judge of its own excellence it never will be the ultimate arbiter. The

perhaps annoying fact is that the principle of absolute sovereignty won't work.

The specialist groups began on the basis of respect for the self-imposed standards of excellence of their mutually chosen members. Did they realize what a profoundly different thing it was to change over to examinations as the basis of recognizing excellence? Why is that a profoundly different system? Because admitting excellence is not the same as excluding incompetence, and because prophesying what may turn out to be excellent, is a far different thing from discovering what has been proved to be excellent. A board of examiners competent to examine on what it already knows, is neither disposed nor competent to examine on what it has yet to learn.

The chance of eventual recognition is a more encouraging circumstance for an original young specialist to deal with, than passing an examination set by those who can withhold approval of the new by insistent emphasis upon expert knowledge of the old. If the specialist groups had continued to elect their members on the basis of recognition of established competence, they would have avoided the serious danger they now run of being the unintentional partners of static and reactionary, albeit powerful and respectable, inertia or ignorance.

In plain truth our medical schools, still fumbling with the first four years of adequate medical education (which we all know is only about half of it), have let the specialists set up examinations in place of teaching, and now who is responsible? The certification boards write prescriptions for schools and hospitals that are neither solvent, nor staffed to provide what is prescribed; and then set examinations that do not and cannot establish the maturity or the competency that certification was intended to guarantee.

Anyone familiar with what the concours system has done to French medicine will be distressed to see American medicine putting its faith and its money on the capacity to pass written and oral examinations. The only competence so proved is the competence to pass an examination. Will obligatory and uniform experience (as soon after graduation as possible) followed by an examination, guarantee such excellence and maturity of judgment as to deserve permanent certification? Let us remember that the earlier the test the more immature the entrants.

If the greatest value for American medicine is to force up the general performance level of all specialists, by tending to the less fortunate, less trained and less gifted, there is much to be said for certification boards. However, another way to raise the general performance level is to exert vigilant and jealous control in behalf of excellence, variety, and freedom to go beyond our present knowledge. The very years you pre-empt for the uniform training for the boards are the most precious in the lives of those young men from whom progress is to come. You can see and I hope you can read, the price tag of the present emphasis upon specialty board examinations.

Another difficulty in the general field of according approval: certification on the basis of prescribed uniform experience, plus passing an examination is, very largely, an example of giving permanent approval for temporary performance. For in a series of specialties changing as rapidly and as continually as those of medicine, to have permanent approval based on temporary performance strikes my somewhat perverse sense of humor as ludicrous. You shaved day before yesterday and it was a nice job, but what about the situation at five today? Some states of grace are not permanent. The certification of a specialist, if his specialty is progressing, might well be limited to a period of 10 years and void thereafter unless validated by obviously excellent performance attested by his equals. We do something similar in obsolescent medical schools. Since I have known deans who hoped for a class B. status for their schools so they could wring money out of their legislatures for real improvements, I could hope that obsolescent specialists might wring concessions from their wives and their hospital boards, to refresh their knowledge and thus recapture the status they have lost.

If the examinations were designed and administered to find out what the candidate knows as a result of years of preparation, there would be some chance of recognizing his ability and accomplishments. But the tradition of examinations in this country is not to find out what a candidate knows, but whether he knows what his examiners know. And that, gentlemen, is a vastly different business in its effect on the candidate before and after the examination, and its effect on the self-assurance of the examiners. A field of knowledge is in a healthy state of cultivation when it is hard to find older men who know as much as the oncoming generation, or even think they do. In stagnant subjects the old always know more than the young and examinations make some sense, when used in moderation.

But there are further difficulties in certification by specialty boards. Their emphasis must be either on education, or upon the mere question of bestowal vs. withholding approval. Even if our medical schools and hospitals were not as far in the red as they are today, the preparation of candidates for certification as specialists would place upon our schools a burden they could not honestly carry without substantial outside help. If the schools, without any other financial support, were to charge what it costs to give the training which certification should require, their training would be so expensive that it would fall to pieces of its own financial weight. Or, worse still, such entrance to good standing as a specialist would increase the cost of becoming a specialist and so increase the excuses given for recovering the expenses later by high specialist fees. This would be unwise, for we are suffering quite enough from the notorious charges of some specialists and we may well be warned that the public is reluctant to give money for the gratuitous education of commercial minds. Would each specialist group tax themselves enough to supply and support enough training centers to renew their ranks? Unless this be feasible or some constant new source

of adequate support be found, the situation seems to me a rather heedless and confused tragi-comedy of hope and hypocrisy.

Perhaps you think the language strong. The intention of specialist certification is to raise the level of the performance of specialists. That seems admirable. But the most important characteristic of truly admirable people is not their credo but that they insist on forever reducing the gap between words and deeds, between the ideal and the actual, between credo and accomplishment. The specialist societies assumed that ever increasing amounts of money would be found to strengthen and enlarge the facilities and the personnel required: but the depression and four years of war came instead. Research experience is not encouraged: the young men usually will jump only the stipulated hurdles. The specialists cannot pay the piper but they have called the tunes, taking to themselves the freedom, and leaving to the schools and hospitals the responsibility.

There is some evidence that the press of candidates for certification has prevented some boards from considering what their long-term policies should be. The seriousness of the situation becomes more apparent when one realizes that in some fields the numbers applying for certification are so large that the only way of reducing the examination to manageable proportions is by the true-false system of examination questions. Sometimes there is too little time to test the clinical competence of a candidate. The power the specialty boards possess is now increased to an uncontrollable degree because hospital boards and government services have discovered the comfort of passing the buck by letting certification be the basis of appointment, and in some cases of salary status. It seems rather naive for anyone to be surprised that lay trustees of hospitals or government agencies are putting a cash value on specialty board certification. Where do you suppose they could have gotten the idea that there is already an "aristocracy" in medicine, if not from the "aristocrats?"

If the specialists would stop to think of how valuable to their welfare is an abundance of well-trained general practitioners, they might pause before giving their unhesitating support to a development that discourages and deprecates general practitioners.

I am going to make a statement about subordinate specialties—so first let me say what I mean by subordinate specialties. They are those specialties whose practice is dangerous without a sound knowledge of medicine and surgery. Putting money and prestige value on certification will certainly result in this: the subordinate specialties will claim independence of internal medicine or surgery. Now we all could save quite a lot of time and bother for ourselves by letting the subordinate specialties disregard the advantages of broad training, but the price tag of this neglect will be outraged public opinion, slow in developing, but strong and reckless in its later stages, and scornful of specialists narrowly trained.

We would do well to regard the present state of specialty certification as a poor substitute for sound thinking and further realistic action. It is,

in part, symptomatic of our outmoded system of state licensure. If the problem is to keep the specialties clean of pretense and incompetence, the Council on Education of the American Medical Association should pass upon the facilities for the teaching-hospital training of candidates, at least as closely as it passes on our medical schools. At present the Council and the Specialty Boards are not adequately inspecting or influencing the quality of residency training given in hospitals as part of the training of specialists. How will they judge the product of their neglect? The National Board of Examiners should administer the examinations but only to candidates who have completed a thorough preparation to the satisfaction of the teachers in schools and teaching hospitals approved by the Council on Education. This would focus attention where it belongs, on the educational aspects of medical education, and not on the self-determined exclusiveness of a series of well-meaning but narrow professional groups.

The National Board could very wisely use the specialists' knowledge and desire to keep their ranks free of incompetents and imposters. The specialty board certification, if it is inescapable, should be continued, but the National Board should have the final authority, if need be, to override a position taken by a specialty board. Why? Because history shows that cliques and factions within a specialty are less dangerous if they must explain their views to other judges than their own prejudices. What would a self-regulating specialty board in surgery have done with the application of young Lister for certification? Can we learn nothing from history? Can we not foresee and forestall the dangers of specialty board certification, where so much power is held narrowly?

On the other hand if the purpose of the specialty boards were to distinguish and reward the merit and accomplishments of specialists recognized as not merely competent, but excellent leaders, then examinations should be dispensed with, as they were at the beginning. When you force Board certification upon virtually all possible candidates by the devices of limiting society memberships, hospital appointments, and appointment or promotion in government service to holders of certificates, you include among your triumphs many young men who would have reached distinction without Board examinations. Indeed they would have succeeded in ways more varied, original and productive of fresh advances, than via the uniformity your best judgment imposes. And while facilitating the entry of the immature who happen to be ambitious, you will forego the membership of more mature men who happen to be as interested in their work as they are in their careers.

If the level of the practice in certain specialties has improved, is it any more likely that certification boards did it, than that the general level of wealth and education was the greater factor in play? Was the patient already mending when the new treatment was begun? Granted that the preparation required for certification is one method by which a doctor can

claim the status of a specialist, it has not been and it is not the only way. Why then reinforce it so heavily with prestige and cash value?

But one really important fact besides the wish to protect the public ought to be realized and utilized: at present the first 10 years of an American doctor's professional life are apt to contain too many hours of waiting to use the skills and knowledge he has acquired. It is an inexcusable waste of the strength, the competence, and the ambition of thousands of young men, able and eager for a better use of their time. That realization, which is not clannish or exclusive, offers the best point of departure in measures to improve the performance of specialists.

It takes 10 years to make a truly competent and responsible doctor. Would it not be useful to back off and regard that 10 year period for what it is—an essential unity? Instead we look at it piecemeal. We have put the first four years in care of the universities and taken a good deal of satisfaction in getting rid of the proprietary schools and the purely professional control they gave to medical education. Examinations for the license to practice helped to strengthen the assumption that four years were enough. But the stubborn fact remained that four years were not enough. Indeed it became increasingly true that four years were not enough. Minnesota with admirable realism insisted on the intern year. Attention began to focus on internships and residencies, but very few medical schools were in a position to assume explicit and extensive responsibility or control of the training given their graduates. The control drifted. And with the rapid rise of board certification, control is drifting still further away from the schools and the teachers of medicine, into the hands of the practitioners via the specialty boards. The task of the next two decades is to put ten-tenths of medical education, not four-tenths, where it belongs.

I have offered these comments because they touch upon something that is tangible and concrete, and because the defects of specialists' certification illustrate a danger to the most precious element in any profession. What is the quint-essential element? The biological commonplace, that when a cell becomes highly differentiated it loses its power of regeneration illustrates my belief that the demands of a highly specialized and exclusive activity endanger the most precious element in any profession—namely its capacity for change and growth, for regeneration and continuity. A powerful and efficient eunuch is nearer to death itself than a corpse with six sons and daughters as pallbearers. The different experiments of Nature show that the infinite variety of what Muller calls "the dance of the chromosomes" is a more tenacious because it is a more variable way of continuing life than mere cellular fission. Freedom is more than a pleasure principle: it is a guarantee of vitality and survival through variety. Every tendency in our profession, especially every trend that seeks to strengthen its position by means of standardization, obligatory uniformity and unvarying acceptance deserves to be challenged as a threat to variety and survival.

At the beginning of this paper I traced the consequences of a dominant and wonderfully rewarding preoccupation with the view that every disease has a single and sufficient causative agent, because I believe with Vannevar Bush that science is an unending frontier, and because even as scientific a concept as unique causation fails to supply the variety that medicine must encourage if we are to go on from here.

We must fend for the future of medicine by protecting its freedom to change and grow. There is no surer way of seeing the potentialities of a given subject than to examine its relation to all that is *not* it, but around it. It is an extension, not a negation, of clinical medicine to explore its own outside relations; the relations, for example, of somatic and organic disease to the findings of psychologists, sociologists, and geneticists. Not only is there an interior milieu for the body, but socially an exterior, and genetically an anterior, milieu. So frequently have we contrasted the individual with the mass that the word "individual" has come to have the connotation of isolation or separation. But the essence of individuality is the uniqueness of the individual's ties to his environment, and the indivisible cohesion or inseparability of these ties. Surely that idea alone points to a gateway outward on uncharted seas and to a variety of new lands.

But there would be an ironical humor if one were to argue for variety and freedom by attempting to list the opportunities. Freedom transcends lists and smiles at outlines. As the Arab chief remarked to Gertrude Bell, "Madam, may I remind you that liberty is never given—it is always taken."

One can, however, speak of preparations for a voyage even when destinations are merely to be presumed, as did Columbus when he left the western shores of Europe. Let us hope that medicine will take the appropriate courses to reach many more than the destinations already presumed—psychosomatic medicine, industrial medicine, social medicine, genetic medicine, rehabilitation, the natural history of disease, growth and aging. So please bear with me as a person given, and perhaps too much given, to abstract thinking, if I offer two hints for those embarking for new destinations in medicine.

One is that we all should make definite efforts to encourage more recording of unexplained phenomena. In comparing American medicine with that in some other countries I have had the impression that we lack a certain kind of scientific candor in that we fail to encourage the observer of inexplicable phenomena. We seem averse to seeing a naked uninvited fact at our feasts of reason. A fact, we seem to feel, should be clothed in at least an hypothesis, or better still in the uniform of experimental confirmation. So the price of our fear of the raw is a dull habituation to the conventional. I make this plea because it is hard enough for a young and original observer even to see what he cannot explain, without having the additional difficulty of formal discouragement from editors and audiences if he attempts to describe and record the obstinate beauty of an unacknowledged, unexplained fact.

The other counsel we should all offer to those setting out for continents unknown, or at least not as yet too much explored, is that they should attach more importance to the mental processes by which they interpret the relationships between the phenomena they observe. There could be rules of evidence in medicine as in law, and our medical schools would demand more rigorous thinking and more critical reading if they were to emulate the better law schools in training students to make the correct inferences from observed events: a course called Evidence. The incapacity to think straight flourishes like a weed in the virgin soil of our rank neglect of the meaning and use of words. This tare is watered by an ignorance of the laws of probability and sunned by callow personal ambitions. Almost never uprooted by a critic who distinguishes between chance, correlation, and the three main types of cause, predisposing, precipitating and perpetuating, this weed—the incapacity to reason—overruns our medical literature and chokes out that rare but almost infinitely valuable plant, whose fruit would nourish us—sound reasoning. With publication so important a means of securing recognition, and with communication so important a tool for the progress of medicine, there is both urgency and importance in fostering a much more discriminating insistence on sound thinking and clear expression in our professional literature. I would not be discouraged at the depressing style of medical writers if such language led them to conclusions that were valid and well knit. And I would not be apprehensive if the journals that carry articles containing any reasoning at all were to appear but twice a year, provided conclusive reasoning was the characteristic of every article printed. But I cannot see satisfactory progress for medicine until we pay explicit and forceful attention to what is proof, what is evidence, in contrast to what is mere linked softness long drawn out.

But the essence of my plea to you has not been hints on procedure, nor criticism of one handicap from which we may suffer increasingly, nor exhortations as to what new goals medicine should set itself. I have suggested that we have been greatly preoccupied during the last two generations with the idea that each disease has its own single, sufficient and specific cause, perhaps so much preoccupied that Medicine must now look to a wider horizon of interests in order to find freedom, and variety for survival. To simple precision of observation we must vigilantly add comprehensiveness of observation, and from familiarity with only simple causation we must advance to a greater complexity and rigorousness of thought. We have crossed, but not fully occupied, an area of pathology and physiology that is continental in its magnitude and variety. In ways that make the comparison not too grandiose we have come to the edge of a continent, to a Golden Gate. Whitehead comparing our times with other periods has said, "This is the largest epoch in human history." Our hope must be that Medicine—which, to include all its branches, we might call Great Medicine—that Great Medicine will go on and out to meet change, to seek variety, and with greater vigilance to purchase and deserve a greater freedom.

CASE REPORTS

PARATHYROID CARCINOMA ASSOCIATED WITH ACUTE PARATHYROID INTOXICATION *

By JOHN H. YOUNG, M.D., and KENDALL EMERSON, JR., M.D.,
Boston, Massachusetts

ACUTE parathyroid intoxication in man has been reported but 10 times^{1, 2, 3, 4, 5, 6} and, except in one instance in which the intoxication was caused by the injection of parathormone,² has always terminated fatally. The case to be reported appears to be the first in which carcinoma of the parathyroid gland was associated with acute parathyroid poisoning. This case is of particular interest in that the patient survived one episode of acute intoxication which was terminated by surgical removal of the gland, only to succumb to a recurrence of the same condition six years later. The purpose of this report is to present a case of carcinoma of the parathyroid, to describe the clinical and pathological aspects of acute parathyroid intoxication and to emphasize the importance of prompt surgical intervention.

CASE REPORT

M. O'G., a 59 year old spinster, entered the Peter Bent Brigham Hospital for the third and final time April 26, 1946, complaining of nausea and vomiting of nine months' duration. Her present illness apparently began in 1926 with the onset of pain in the arms, legs, back and ribs. Examination in the Outpatient Department in 1928 revealed obvious stooping and shortening of the body. Roentgen-rays of the spine showed a diffuse atrophy and collapse of several dorsal vertebrae with coarse trabeculation of the pelvic bones. The serum calcium level was found to be 15 mg. per 100 c.c., and a diagnosis of hyperparathyroidism was made. The patient refused further study at this time, and was placed on calcium lactate, 25 grains daily by mouth, and cod liver oil. In 1932 a urinalysis showed a specific gravity of 1.030 with no albumin and a normal sediment. She continued to feel fairly well until 1938 when she fractured her right elbow in a fall downstairs. While recovering from this accident she experienced her first attack of nausea and vomiting which subsided spontaneously in about three weeks. The fracture healed slowly and the patient remained comparatively well until May, 1940, when nausea and vomiting recurred. These became progressively more severe during the next three months until she was unable to retain even water. The vomiting was unassociated with meals and there was no complaint of abdominal pain. She also noted polyuria, increased thirst, and weight loss of 28 pounds in the five months prior to admission to the Medical Service, on October 1, 1940.

The past history was of interest in that the patient had had a popliteal angioma removed in 1899 with subsequent paralysis of the left peroneal nerve and atrophy of the left lower leg. Ten years later she had an operation for a deformity of her right foot. In 1909 she spent three months in a sanatorium following a pulmonary hemor-

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From the Departments of Pathology and Medicine, Harvard Medical School, and the Medical Clinic, Peter Bent Brigham Hospital, Boston.

rhage. The diagnosis of tuberculosis was never proved and she was discharged cured. Except for a deficiency of milk, her dietary history seemed adequate. In 1920, she was incapacitated for four months with swelling and pain in her joints which subsided without recurrence.

Physical Examination. At the time of admission in 1940, the temperature was 98.6° F., the pulse 78, the respirations 20, and the blood pressure 160 mm. Hg systolic and 88 mm. diastolic. The patient was moderately dehydrated. There was scoliosis and kyphosis of the dorsal spine, limitation of extension of the right arm, atrophy of the left leg, and ankylosis of the left ankle. Several hard masses were palpated in the muscle just above the left popliteal space. A hard, marble-sized mass was palpated in the lower pole of the thyroid. The reflexes were hyperactive. The remainder of the physical examination was negative.

Laboratory Data. The urine had a specific gravity of 1.010 and contained 1+ albumin and numerous red and white cells. The Sulkowicz test was 4+. The hemoglobin was 95 per cent and red blood cell count 4,860,000 per cu. mm. These values fell to 68 per cent and 3,800,000 per cu. mm. respectively on restoration of a positive fluid balance. The serum calcium concentration was 22.4 mg. per 100 c.c. This is one of the highest values yet reported in man and approaches the maximum levels reported by Cantarow, Stewart, and Housel⁷ in dogs fatally poisoned with parathormone. The serum concentration of phosphorus was 3.4 mg., of phosphatase 10.6 Bodansky units and of protein 7.7 gm. per 100 c.c. The serum chloride level after hydration was 77 m. eq. per liter. A urea clearance test averaged 20 per cent of normal and the phenolsulfonphthalein excretion was markedly delayed, with a total of 25 per cent in two hours. The blood non-protein nitrogen ranged from 31 to 61 mg. per 100 c.c. Roentgen-rays showed extreme generalized osteoporosis, soft tissue calcification of the left hamstrings and definite cystic areas in the distal end of the right humerus. No renal calculi were seen and there was no roentgenographic evidence of intrarenal calcification. Cystoscopic examination revealed a chronic cystitis and evidence of bilateral chronic pyelonephritis.

Hospital Course. The patient continued to have intractable vomiting, and on the fourteenth hospital day, the diagnosis of hyperparathyroidism having been established beyond reasonable doubt, the region of the left lobe of the thyroid was explored under local anesthesia. Two masses, 2 by 2.5 and 3 by 3.5 cm., were found adherent to the thyroid. To expose the deeper of the two masses, it was necessary to remove the left lobe of the thyroid. There were adhesions around this accessory tumor; it was separated with difficulty from the esophagus, and the left recurrent laryngeal nerve which ran through its substance had to be sacrificed.

Postoperatively the patient did well. The vomiting promptly ceased and the bone pain which had been a consistent part of the picture gradually diminished. The serum calcium level fell to 13.0 mg. per 100 c.c. in 48 hours and to 11.4 mg. per 100 c.c. the fourth postoperative day, at which time the serum phosphorus level was 1.24 mg. per 100 c.c. and the Sulkowicz test on the urine was negative. At no time was there any sign of tetany. She was discharged on the tenth postoperative day on a diet high in calcium, phosphorus, and protein.

Grossly the specimen removed at operation consisted of an irregularly shaped tumor and a portion of normal thyroid. The tumor weighed 5.8 gm. It was composed of a solid mass of soft, delicately lobulated, pinkish-gray tissue and several cysts. One cyst, which measured 1.9 cm. in diameter, had a thick fibrous wall and there were several papillary projections of tumor into its cavity. There were several small, thin-walled cysts which measured less than 3 mm. each.

The specimen was fixed in acetic Zenker's solution, formol Zenker's formalin, and absolute alcohol, and stained with eosin and methylene blue, hematoxylin and eosin, phosphotungstic acid and hematoxylin, Mallory's aniline blue, Best's carmine, and Weigert's elastic tissue stains.

Microscopically the tumor was composed of round and oval, compact masses of cells, separated by interlacing columns of collagenous connective tissue which branched into fine anastomosing strands, the whole having a lobulated appearance (figure 1). There were many thick-walled vessels in the larger septa with a rich capillary network in the large masses of tumor cells. The tumor mass was surrounded by a fairly thin capsule composed of loose connective tissue. The tumor had invaded the

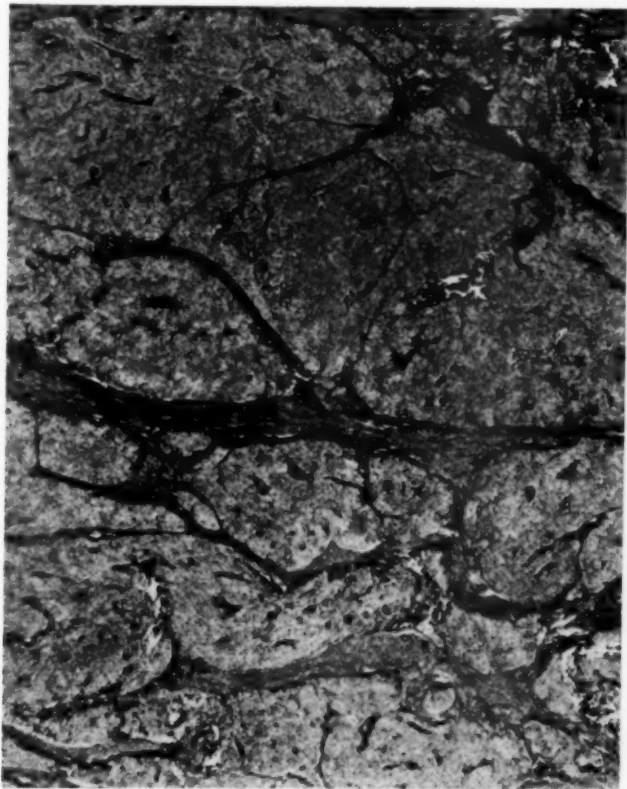


FIG. 1. The parathyroid tumor removed at operation. Note the lobular character. Magnified 43 times. Mallory's aniline blue.

capsule at several points. The thick cyst wall was composed of laminated, acellular bundles of collagenous connective tissue. Small papillary processes projected from the cyst wall into the lumen. These were formed of loose connective tissue cores and covered with epithelial cells.

The masses of compact tumor cells showed a striking perithelial arrangement. In several instances there was also a suggestion of palisading of the cells along the septa. In no place were acini apparent. The tumor cells were in direct contact with

many of the capillaries. The tumor was seen invading veins, capillaries, and lymphatics.

The major portion of the tumor consisted of large, polyhedral cells with distinct basophilic cell borders (figure 2). There was abundant, finely granular, faintly eosinophilic cytoplasm. The cytoplasm of some of the cells was pale and a few cells showed clear halos about the nuclei. The Best's carmine stain demonstrated a small amount of glycogen in minute droplets in many of the cells. The nuclei were ec-

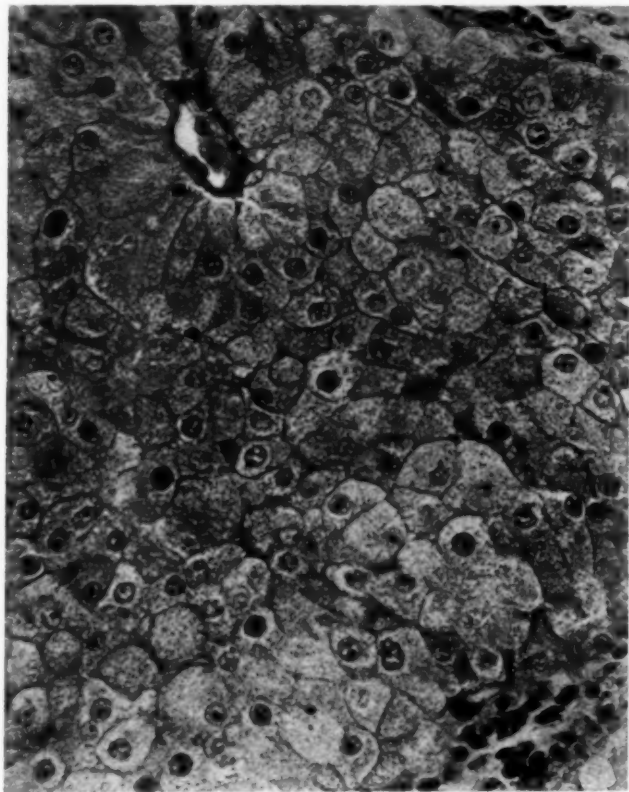


FIG. 2. Higher power of surgical specimen. Magnified 480 times; eosin-methylene blue.

centric, vesicular and contained varying amounts of chromatin. The nuclear membranes were prominent and basophilic. In most of the nuclei the chromatin was finely granular and evenly distributed. There were usually two to three dark nucleoli. Occasionally the nuclei were pyknotic but no mitotic figures were seen.

The patient was followed in the Outpatient Department for the next four and one-half years. She was treated with calcium gluconate, 4 gm. daily and improved markedly both subjectively and objectively for three years. She felt well enough to

work in the garden, most of her bone pain disappeared, and she gained 35 pounds. During this time there were no urinary symptoms. The blood pressure varied from 148 to 164 mm. Hg systolic and 74 to 100 mm. Hg diastolic. Roentgen-rays taken during this period showed progressive evidence of new bone formation.* The calcium and phosphorus levels were as follows: in 1941, the serum calcium concentration was 10.0, and the phosphorus, 2.4 mg. per 100 c.c. In the latter part of 1942, the calcium level was recorded as 11.8, the phosphorus was 0.9 mg. per 100 c.c., and the patient became more easily fatigued. In May of 1943, the serum calcium concentration was 13.0 and the phosphorus 2.48 mg. per 100 c.c. At this time the patient complained of lack of energy and pain in the right hip, and from this time on there was failing vision and gradual loss of weight. By 1945 she was incapacitated by bone and joint pain and had lost 22 pounds. The serum calcium was 16.8 and the phosphorus was 3.1 mg. per 100 c.c.

The patient failed to return for follow-up and was not seen until April of 1946 when she was admitted to the hospital because of persistent nausea and vomiting of nine months' duration. During this time, 16 days was the longest period that she had gone without vomiting. She had had constant bone pain similar to the pain she had experienced prior to her first operation. In November 1945, she had fractured her right humerus just above the elbow as she raised her arm to grasp a banister. This was the first fracture that she had suffered since her operation. Three weeks before entry the patient thought she had heard several ribs crack while coughing. This was followed by chest pain which was aggravated by breathing.

Physical Examination. The temperature was 99.6° F., the pulse 68, the respirations 24, and the blood pressure 120 mm. Hg systolic and 50 mm. diastolic. The physical examination at this time showed extreme dehydration and lethargy. She was unable to sit up in bed because of pain in all the extremities. There was generalized bone tenderness and a non-united fracture of the right humerus. The eye-grounds showed only minimal arteriosclerotic changes. The heart and lungs were essentially normal. No masses were palpable in the neck.

Laboratory Data. The urine attained a maximum specific gravity of 1.012 after the injection of 1 c.c. of pituitrin. It contained 2+ albumin and numerous white cells. The Hinton test was negative. The hemoglobin on admission was 12.8 gm. per 100 c.c., falling to 8.4 gm. per 100 c.c. after the patient had become hydrated. The hematocrit was 34 per cent at the time of admission. The white count varied between 2700 and 8000 with a normal differential. The blood urea nitrogen level was 44 mg. per 100 c.c. and plasma protein concentration 6.1 gm. per 100 c.c. The fasting blood sugar level was 111, serum cholesterol 316, calcium 13.8, and phosphorus 4.3 mg. per 100 c.c. The serum phosphatase was 25 Bodanski units. Two phenolsulfonphthalein tests averaged 8 per cent excretion after two hours and the urea clearance was 10.5 per cent of normal. Roentgen-rays revealed the characteristic bone changes of hyperparathyroidism, even more pronounced than before the patient's operation in 1940. A 24 hour urinary calcium excretion was 382 mg. at a time when the patient's calcium intake had been negligible for several days.

The changes in serum electrolytes are shown graphically in figure 3. The admission serum level of chloride was 114 m. eq. per liter and the serum carbon dioxide combining power was 12.7 mM. per liter. During the next three days, following the parenteral administration of glucose, saline and sodium bicarbonate, the serum carbon dioxide combining power rose to 17 mM. per liter, but the serum chloride concentration fell to 81 m. eq. per liter. More intensive therapy with intravenous saline

* We have avoided the terms decalcification and recalcification because of the erroneous impression these terms convey. Enchondral bone is formed by the deposition of bone matrix (osteoid) which is subsequently calcified. When resorption takes place, the bone matrix as well as the mineral salts are removed. Therefore, the bone matrix must again be laid down before recalcification can take place.

and sodium lactate succeeded in restoring a normal serum chloride level although the carbon dioxide combining power never reached normal.

Hospital Course. In spite of continued efforts to restore and maintain a normal electrolyte balance in order to prepare the patient for operation, she continued to have intractable vomiting. For the first 10 days she ran an irregular fever as high as 103° F. Thereafter, her temperature remained below 100° F. The blood urea nitrogen concentration remained between 35 and 45 mg. per 100 c.c. throughout her

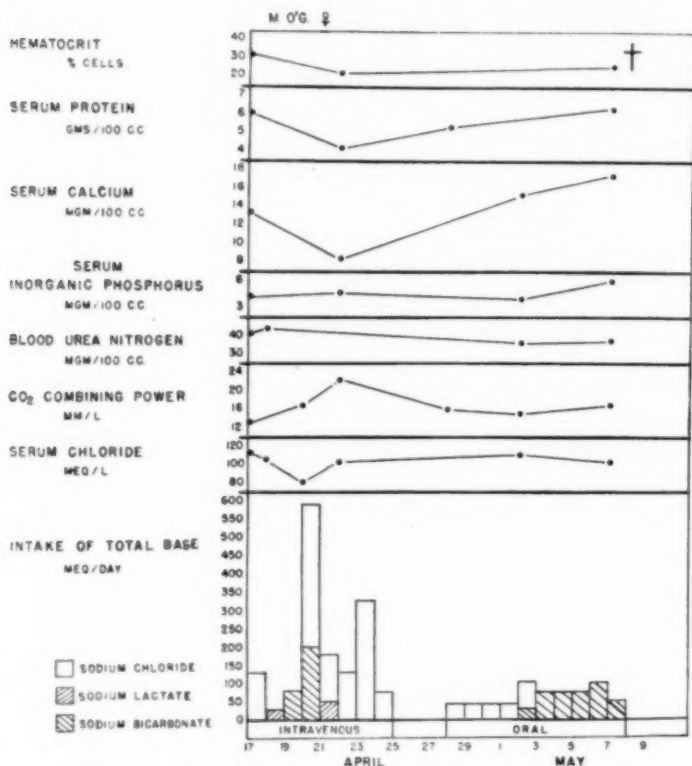


FIG. 3. Terminal changes in hematocrit, serum protein, urea and electrolytes in patient M. O'G.

hospital stay. The hematocrit fell to 23 per cent and continued at that level. The serum protein level after falling to 4.2 during the initial period of hydration gradually rose to 6.4 gm. per 100 c.c. The serum level of calcium rose from 13.8 to 17.6 and of phosphorus from 4.2 to 6.0 mg. per c.c. during the third week following admission. On the twenty-third hospital day the patient's general condition seemed unchanged. During the night, however, her pulse suddenly became imperceptible, she lost consciousness, took a few deep respirations and died.

Autopsy Findings. The body was that of a well developed, fairly well nourished, white female which measured 141 cm. in length. The left foot was smaller than the right with a slight inversion deformity. There was a right dorsal, left cervical scoliosis. There was a very large, bony hard mass behind the left knee just above the popliteal space. This was incorporated in the muscle tissue. It weighed 150 gm. and consisted largely of bone. There was a hard mass attached to the bone in the



FIG. 4. Pulmonary artery showing medial calcification. Magnified 100 times. Von Kossa's silver nitrate.

supracondylar region of the right elbow. The peripheral vessels were calcified and tortuous.

The body cavities showed no abnormalities. The heart was normal except for calcification of the coronary arteries. The lungs showed edema. The spleen weighed 320 gm. There were several cavernous hemangiomata and a recent infarct. The gastrointestinal tract, pancreas and liver were normal. The gall-bladder contained no stones but showed the white reticulated pattern of cholesterosis.

The kidneys weighed 120 and 130 gm. The capsules were only slightly adherent. The external surfaces were coarsely granular with small, shallow, finely granular scars. Longitudinal sections of both kidneys showed the cortex and medulla of each to be well demarcated. The cortices averaged 0.5 cm. in width. The tubular striations were accentuated by small deposits of calcium. The vessel walls were thickened.

The adrenals weighed 11 and 14 gm., but were not remarkable. There was a cervical polyp and several leiomyomas of the uterus and some of these were calcified.

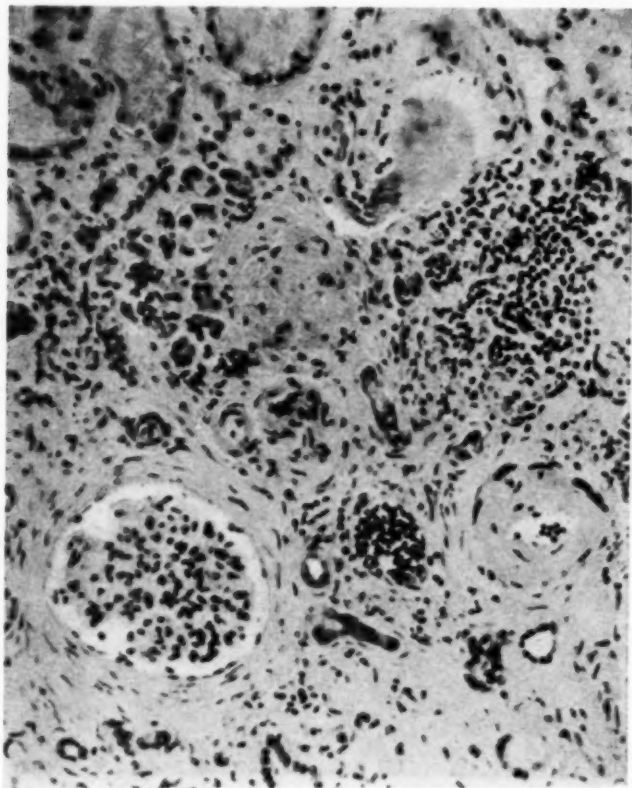


FIG. 5. A section of the cortex of the kidney showing typical chronic changes. Magnified 220 times. Eosin-methylene-blue.

The ovaries were atrophic. The aorta was markedly atheromatous and calcified, especially distal to the renal arteries. The vena cava and tributaries were unremarkable.

The left lobe of the thyroid was not present. The right lobe weighed 14.5 gm. and appeared normal. There was a firm mass of tissue concealed beneath the left sternocleidomastoid muscle. This was adherent to the posterolateral aspect of the larynx and esophagus. The mass was egg-shaped and measured 3.5 by 2.5 by 2.5 cm.

It weighed 10.0 gm. and was covered by a thin, shaggy, fibrous capsule. On cross-section, it was gray and lobulated and had a dense fibrous stroma. Normal parathyroid glands were not located.

The skeletal system showed generalized fragility and softening. The cortex was markedly thinned and the medulla was soft and mushy. Examination of the brain was negative.

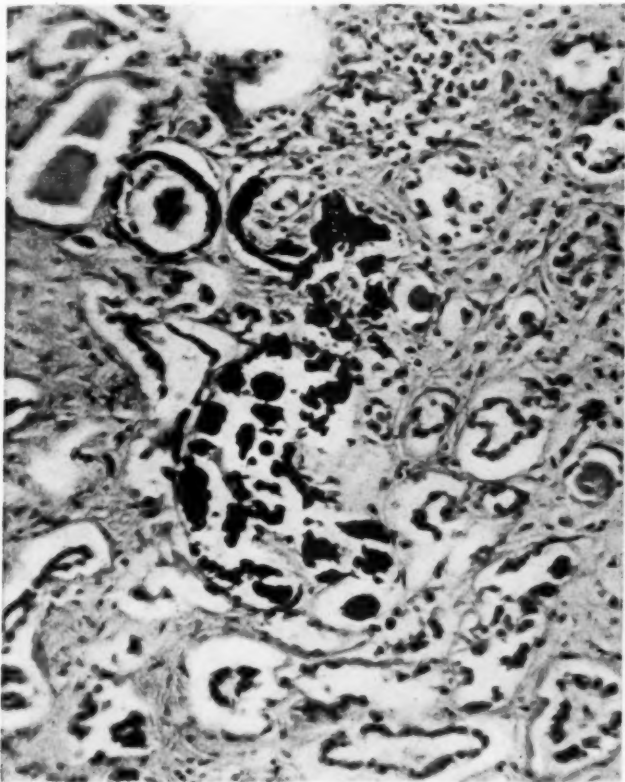


FIG. 6. A section of kidney showing calcification in and about the tubules. Magnified 240 times. Hematoxylin and eosin.

Microscopic Examination. Routine sections were fixed in acetic Zenker's and stained with eosin-methylene-blue. Additional blocks were stored in formalin and special stains done when indicated.

Sections of the heart showed the epicardium and endocardium to be negative. There were areas of fibrosis in the myocardium which were focal in some areas and diffuse in other areas. There were deposits of calcium in the media of some of the medium sized arteries. There was hyaline intimal thickening of the larger coronary arteries.

The sections of the lungs showed considerable edema. The striking feature was the rings of calcium in the walls of the arteries of varying sizes (figure 4). Large deposits of calcium were seen throughout the media. A few polymorphonuclear leukocytes and lymphocytes were found about some of the calcium deposits. Some of the larger arteries showed small areas of fibrosis about them. The vessels also showed hyaline intimal thickening. There was no calcium in the bronchial walls.

The capsule, trabeculae, and Malpighian bodies of the spleen were not remarkable. There were many polymorphonuclear leukocytes scattered in the red pulp. One area, several millimeters in diameter, was infarcted. A fresh thrombus was seen in a medium sized artery. In the sections two cavernous hemangiomas were seen. The

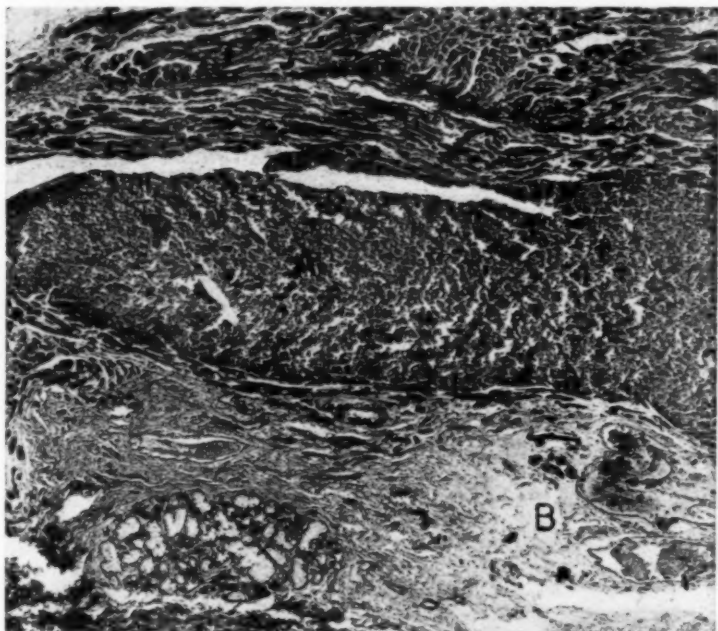


FIG. 7. A. Tongue of tumor invading esophageal muscle. B. Tumor in veins. Magnified 43 times. Eosin-methylene-blue.

pancreatic acini and islets of Langerhans appeared normal. There was a small amount of squamous metaplasia of the ductile epithelium and a few dilated ducts. The vessels showed hyaline intimal thickening but no calcification. The liver was normal. The tips of some of the mucosal folds of the gall-bladder were swollen with deposits of cholesterol. There were a few small collections of lymphocytes in the submucosa.

Sections of kidney were stained with eosin-methylene-blue, hematoxylin and eosin, phosphotungstic acid-hematoxylin, Weigert's elastic tissue stain and von Kossa's silver nitrate stain for calcium. The striking feature was the diffuse fibrosis of the interstitial tissue. This was seen surrounding all of the tubules and glomeruli

(figure 5). There was a diffuse infiltration of chronic inflammatory cells. Deposits of calcium were present in the lumina of the proximal convoluted tubules and, in some instances, were present in the interstitial tissue beneath the tubular epithelium (figure 6). No areas of necrosis were noted. Many of the tubules were dilated and showed degenerated epithelium. Most of the glomeruli showed pericapsular fibrosis and many of the glomerular tufts were hyalinized. There was hyaline intimal

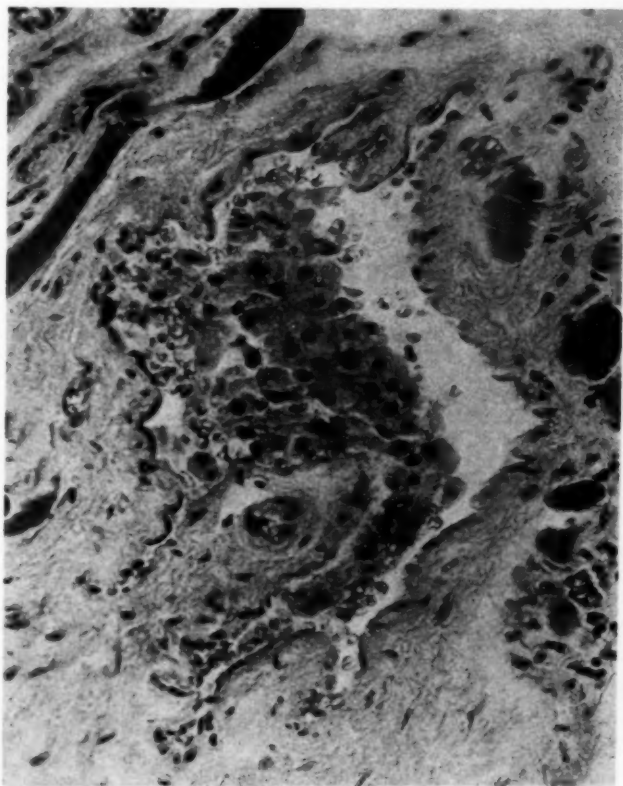


FIG. 8. Vein at periphery of tumor showing invasion by tumor. Note muscle bundles about vein. Magnified 300 times. Eosin-methylene-blue.

thickening and reduplication of the elastica of the larger vessels. Many lymphocytes were present beneath the epithelium of the calices.

The endometrium was not remarkable. Some of the vessels of the myometrium had deposits of calcium in their walls. The section of one leiomyoma showed large areas of bone. There was a cervical polyp.

Eight blocks of the parathyroid tumor were fixed in acetic Zenker's formalin, and absolute alcohol, and embedded in paraffin. The sections were stained with eosin-

methylene-blue, hematoxylin-eosin, Weigert's elastic tissue stain, Mallory's aniline blue, phosphotungstic acid-hematoxylin and Best's carmine. The general lobulated architecture found in the surgical specimen was preserved in the tumor at autopsy. Interlacing bands of thick collagenous connective tissue enclosed islands of tumor cells. The tumor cells had lost the perithelial arrangement which was so striking in the surgical specimen. There were several large areas of necrosis and many collections of lymphocytes scattered throughout the stroma.



FIG. 9. Vertebra showing osteitis fibrosis cystica generalisata. Magnified 118 times. Hematoxylin and eosin.

The cytology of the two specimens was difficult to compare because of the different lengths of time intervening before fixation. The cells in the autopsy specimen were large and polyhedral. There was abundant granular eosinophilic cytoplasm. No cells with clear cytoplasm were seen. Best's carmine stains showed no appreciable amount of glycogen. The nuclei were hyperchromatic; however, no mitotic figures were seen.

The tumor was found deep in the esophageal muscle close to the submucous glands (figure 7). Masses of cells were demonstrated in many veins and lymphatics (figure 8). These almost occluded the lumina and conformed to the shape of the vessel wall.

Paraffin and celloidin blocks of vertebra, ribs, femur, sternum, skull and ilium were prepared. These were stained with eosin-methylene-blue, hematoxylin and eosin, phosphotungstic-hematoxylin, and Mallory's aniline blue (figure 9). The cortical bone was much thinner than usual. The Haversian canals were so increased in size that there were only thin columns of bone between them. There were large multinucleated osteoclasts seen adjacent to the thinned cortex and close by orderly arranged osteoblasts. The areas between the narrow columns of bone were filled with a young, loose connective tissue. Normal marrow remained in some areas.

The calcified mass of bone in the substance of the muscle was essentially similar to the skeletal bone. However, the columns of bone appeared thicker and the osteoclasts were fewer in number. There was fibrous replacement of the absorbed bone.

Sections of the cerebral cortex, basal ganglia, pons, medulla, cerebellum and cord were examined. No abnormality was noted. No other significant findings were noted upon examination of the gastrointestinal tract, adrenals, urinary bladder, ovary or breast.

DISCUSSION

The pathologic findings in this case were of considerable interest. The parathyroid tumor was considered to be a carcinoma because it was found invading the esophagus, blood vessels and lymphatics, and had recurred after surgical removal. There have been 38 cases of carcinoma of the parathyroid gland reported up to 1946. The literature has been carefully reviewed by Norris¹² and will not be analyzed here. Norris accepted 12 of these 38 cases as carcinoma; three he considered questionable, while 23 he believed were wrongly diagnosed.

The other findings were those to be expected in a patient suffering from long standing hyperparathyroidism. The changes found in the kidney were similar to those described by Albright, Baird, Cope and Bloomberg⁸ and Anderson.⁹ The bone changes were those of osteitis fibrosa cystica generalisata (Albright). There was extensive metastatic calcification in the arteries, muscle, and uterus.

Acute parathyroid intoxication may be defined clinically as that stage of hyperparathyroidism wherein weakness, lethargy and intractable nausea and vomiting occur in association with an extreme elevation of the serum calcium level, often leading to death without apparent cause unless the hyperfunctioning tissue is removed.

Several theories have been advanced to explain the sudden death in this condition. Cantarow, Stewart and Housel⁷ have described changes in various organs of dogs, particularly the heart and kidneys which they attribute to a direct toxic action of parathormone. This allegedly precedes the deposition of calcium and is somewhat similar to the toxic necrosis induced experimentally in vitamin D poisoning. These authors do not believe this effect is caused directly by the high serum calcium.

Shelling, Kajdi and Guth¹⁰ have shown clearly in dogs that parathormone in repeated doses brings about a marked diuresis of water, chloride and fixed base with resultant dehydration, shock, azotemia and death. These authors were able to prevent a fatal outcome by the administration of large quantities of sodium chloride to replace the urinary loss.

Finally, it is possible that renal insufficiency resulting from fibrosis and calcification of the kidneys may be the cause of death in acute hyperparathyroidism as it is in the chronic form of the disease.

None of these theories can explain satisfactorily the cause of death in the present case. There was no pathological evidence of any unusual toxic necrosis. The heart itself revealed no more than the amount of intimal thickening of the coronaries which might be expected at this age. Medial calcification of the smaller arteries was present, but there was no necrosis or calcification of the myocardium. Although the renal insufficiency noted clinically and the kidney damage observed at autopsy undoubtedly played an important rôle in causing death, the degree of functional renal damage was not sufficient to account for death at the time and in the manner in which it occurred.

An excessive loss of serum base was unquestionably present during both episodes of acute parathyroid intoxication in this patient, as shown by the low level of serum chloride and carbon dioxide combining power and the excessive loss of chloride in the urine. Nevertheless, at the time of death there was no sign of progressive dehydration or increasing azotemia. Replacement of fluid and electrolytes failed to avert death, as it should have done according to Shelling's hypothesis.

We are left with no satisfactory explanation for the cause of death in this case. One possible finding of significance should be pointed out, however; that is, the rapid rise in serum calcium concentration during the last weeks of life. The effect of calcium in increasing the duration of cardiac systole and the opposite effect of potassium in inhibiting cardiac muscular irritability are well known. Hueper¹¹ in 1927 made the suggestion that in parathyroid poisoning cardiac systole might be prolonged to such an extent that congestive failure and circulatory collapse would result. It seems possible that the relatively sudden increase in the concentration of calcium perfusing the heart muscle in this patient may have increased cardiac muscular irritability to the point where ventricular fibrillation ensued. The calcium effect may well have been potentiated by the washing out of potassium incident to the administration of the large amounts of sodium salts which were given to combat the acidosis.

Whatever the cause of death, however, it is apparent in retrospect that this patient should have been operated on immediately under local anesthesia, without delaying in the futile attempt to correct a chemical imbalance the nature of which is not clear. The wisdom of this procedure is amply demonstrated by the dramatic improvement in this patient following operation in 1940 at a time when her serum calcium concentration had risen to 22.4 mg. per 100 c.c., a value comparable to that seen in fatal parathormone poisoning in dogs and reported by Hanes³ in a fatal human case. In the present state of our knowledge the discovery and removal of a hyperfunctioning parathyroid tumor offers the only chance of survival in a similar circumstance.

This case, in respect to its pathology and recurrence, is quite similar to a patient now being followed by Lesses, Schlesinger, and Ober¹² at the Beth Israel Hospital. Their patient has had a locally invasive carcinoma of the parathyroid gland resected three times in two and one-half years. Each time the serum calcium returned to normal and then rose as the tumor recurred. Norris believes, and it is further emphasized by this case and the patient at the Beth Israel

Hospital, that, whenever possible, these tumors should be radically resected if recurrences are to be avoided.

SUMMARY

A case of parathyroid carcinoma associated with long standing hyperparathyroidism and acute parathyroid intoxication is presented. The serum calcium level is one of the highest values reported in man. The theories of the mechanism of sudden death in parathyroid poisoning are discussed. It is suggested that the treatment of choice for parathyroid intoxication is prompt surgical intervention. It is emphasized that radical resection of parathyroid carcinomas should be employed where possible.

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PULMONARY EDEMA IN THE COURSE OF TREATMENT OF MULTIPLE SCLEROSIS WITH PROSTIGMINE: A REPORT OF TWO CASES*

By E. ADELSON, M.D., and F. BRUNN, M.D., *New York, N. Y.*

WIDESPREAD use of prostigmine has shown it to be a useful drug. Like all other powerful medications, its administration is associated with occasional untoward side reactions. In the following, we are reporting our observations on two cases of multiple sclerosis in which pulmonary edema occurred in the course of treatment with prostigmine. Careful review of the literature reveals only one case⁵ of multiple sclerosis complicated by pulmonary edema and no instances of pulmonary edema attendant upon prostigmine therapy. It is perhaps appropriate to mention that we have seen several patients in the past with multiple sclerosis who, while under treatment with prostigmine, developed respiratory embarrassment and moist râles in both lungs. At that time, we were unable to classify the conditions. In the two cases reported below, however, pulmonary edema was manifest.

CASE REPORTS

Case 1. E. D., a 40 year old, white male speech teacher, was admitted February 17, 1947, with chief complaints of inability to walk, difficulty in speaking, defective vision and tremors on purposive movement of the upper extremities. His illness began in 1932 when he had areas of transitory numbness under his nose and on his left temple. The next year, he developed diplopia which lasted two months, and in 1936, his left foot began to drag and slap the ground. Progressive weakness and tremors intensified by voluntary movement gradually involved his neck and all four extremities. For four years before admission vision had been deteriorating; for three years he had had occasional urinary incontinence.

He had no complaints referable to his cardiovascular system nor any history of rheumatic fever. Past history and family history were non-contributory.

Neurological examination revealed the following: Marked head tremor, scanning speech, vertical and horizontal nystagmus and temporal pallor of the optic discs; pupils reacted well to light and in accommodation; there was marked ataxia in the upper extremities; considerable spasticity was present in the lower extremities; deep tendon jerks were hyperactive, abdominal reflexes were absent; there were bilateral Hoffmann and Babinski signs and ankle cloni. Diminished vibratory sensation over the left iliac crest constituted the only sensory disturbance. Spinal tap revealed an initial pressure of 180 mm., final pressure of 110 mm. after removal of 10 c.c. of fluid, 62 mg. of protein, and a colloidal gold curve of 01110000. Diagnosis was made of multiple sclerosis.

Systemically, there were no pathological findings. The heart sounds were normal, and no murmurs were heard. Lungs were clear on auscultation and percussion. Chest roentgen-ray showed the heart to be normal in size, contour and position. Electrocardiogram was normal. Blood pressure on admission was 130/86. Decholin time was 10 seconds. Pulse rate remained between 80 and 90. Urine and blood morphologies and chemistries were normal.

Therapy consisting of prostigmine, 15 mg. t.i.d. by mouth was begun February 22, 1947 and given daily until February 26. In the evening of this date, he received

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From the Department of Neurology, Goldwater Memorial Hospital.

a soapsuds enema of about two quarts. A minute or two after that, he became acutely ill, developing the picture of acute pulmonary edema. He gasped for air, became clammy and cyanotic, and white foam poured from his mouth and nose. Showers of moist râles were heard over both lungs. Blood pressure was 140/80; pulse was 60. He was given morphine sulfate, gr. 1/6 by hypodermic, oxygen, and tourniquets were wrapped around his extremities. He responded slowly, and about six hours later, his chest was practically clear. The patient was conscious throughout the attack and complained of no pain. Blood pressure from his admission until the present time has not changed. His electrocardiogram also has not changed.

Prostigmine therapy was discontinued. Two weeks later, a two-quart soapsuds enema gave no symptoms.

On July 13, 1947, he was again given oral prostigmine, 15 mg. twice a day, by another staff member. On November 29, 1947, he developed another attack of typical pulmonary edema, in every respect similar to, but somewhat milder than the original.

Case 2. T. L., a 47 year old white woman, was admitted July 13, 1939, with chief complaints of loss of vision in her right eye for three years and inability to walk and to use her fingers and hands for two years.

Neurological examination revealed the following findings: Complete optic atrophy in the right eye and temporal pallor of the left disc; normal, reactive pupils; weakness of the entire left side; hyperactive reflexes in the left lower extremity, sluggish reflexes in the right upper extremity, absent abdominal reflexes; bilateral Babinski and confirmatory signs and bilateral Hoffmann signs; ataxia of the right lower extremity; no sensory changes. A diagnosis of multiple sclerosis was made. The patient's condition progressed until 1945, at which time she had spastic paraplegia, hyperactive reflexes throughout and a loss of vibration and position sensations in upper and lower extremities. Spinal tap in 1940 was within normal limits.

There were no complaints of cardiovascular symptoms; no history of rheumatic heart disease. Past and family histories were not significant.

General physical examination revealed no pathologic abnormalities. There were no heart murmurs, and lungs were clear on percussion and auscultation. Chest roentgenogram and electrocardiogram were normal. Blood pressure was 134/86. Pulse ranged between 80 and 90. Barium enema showed a megacolon. Blood and urine examinations were normal.

From December, 1946, she received prostigmine orally 15 milligrams t.i.d. until January 5, when it was increased to 30 milligrams four times a day. This was levelled off at 25 milligrams four times a day on January 20, and she was maintained on this dosage until March 1. In the morning of March 1, while receiving an oil retention enema, she became restless, perspired profusely, developed tracheal rattling which could be heard at a distance and foamed at the mouth. Numerous râles were heard over both lungs. Heart rate was 60. She responded to the same treatment mentioned previously, viz., morphine sulfate, oxygen and tourniquets. Neither blood pressure nor electrocardiogram was changed after the attack.

COMMENT

The majority of all cases of pulmonary edema occur in cardiovascular disease; left ventricular failure is usually considered to be the chief direct cause. Pulmonary edema, however, may be found in a variety of other conditions in which the heart is free from disease, and in which the mechanism of its development is evidently different.

According to current textbooks, pulmonary edema may occur as a result of mechanical disturbances in the pulmonary circulation (embolism, tumor, etc.),

inflammation of the lungs (pneumonia), disturbances in the vasomotor apparatus, chemical irritation (contact with poisonous gases); or finally, injection of substances like chloral hydrate, muscarin, adrenalin, morphine, etc. There are also case reports¹ of pulmonary edema in drowning, after paracentesis of thoracic or abdominal cavities, in shock (electric, anaphylactic, insulin), beri-beri, thyroid crisis, nephritis, uremia, etc. Recently, a case was reported² in which laceration of the lung was followed by pulmonary edema. There is, furthermore, a considerable number of observations to the effect that this condition may occur in the course of diseases of the central nervous system.^{3, 4} It has been reported in cases of trauma to the skull, brain injury, brain tumor, cerebral hemorrhage, meningitis, encephalitis, tabes, poliomyelitis, etc.

To our knowledge, multiple sclerosis complicated by pulmonary edema has been reported only once.⁵ The patient in question had dyspnea, râles over both lungs, tracheal rattling and a temperature ranging between 100° and 104° F. for several days. At necropsy, patches of bronchopneumonia were found. The diagnosis of pulmonary edema in this case is not beyond doubt.

More is known concerning the relationship between administration of prostigmine or physostigmine and subsequent pulmonary edema, although these drugs have been given in innumerable cases without any ill effects. In laboratory animals, pulmonary edema is a usual finding in poisoning by cholinergic drugs in general.⁶ Action of prostigmine or physostigmine has been divided into nicotinic and muscarinic components.⁷ The more prominent effects of stimulation of respiratory glands and the constrictor effect on the muscles of the bronchi are collectively comprised in muscarinic action. Muscarine itself produces pulmonary edema, which in experiments⁸ was found to be characterized by fall in blood pressure, bronchoconstriction and overfilling of pulmonary vessels; atropine and adrenalin relieved the bronchospasm and spared the animal's life. True, hyperacute secretion of respiratory glands may by itself produce the clinical picture of edema of the lungs; microscopic evidence indicates, however, that cholinergic drugs lead to true pulmonary edema with transudation into the alveoli.⁶

The constriction of bronchial muscles is regarded as a potent factor in the development of edema.⁹ The assumption is that bronchial constriction and increased secretion of respiratory glands impede free inflow of air. Consequent anoxia renders the dilated pulmonary vessels more permeable, and then the suction of the descending diaphragm on the incompletely closed mechanical system draws fluid from the vessels into the alveoli. It was claimed¹⁰ that the bradycardia caused by prostigmine or physostigmine induces dilatation and consequently increased permeability of the pulmonary vessels.

Additional light is thrown upon the connection between the autonomic nervous system and pulmonary edema by the experience gained from experiments and operations on the autonomic nervous system in the neck. Bilateral vagotomy in the neck is known to be followed by pulmonary edema after one or two days. It develops almost immediately if the operation is accompanied by an intravenous infusion of saline.¹¹ In a case¹² of cancer of the esophagus, both vagi were crushed during bouginage of the stricture. Fatal pulmonary edema developed within half an hour. On the other hand, injection of the vagus with procain¹³ has been used with success to relieve pulmonary edema in cardiac patients. It may appear paradoxical that cutting the vagi gives opposite effects from blocking them with procain; however, one has to consider that these procedures may

give different results, because cutting may involve an initial stimulus. Another difference may lie in the selective affinity of procain for nerve fibers of different quality. The theory^{14,15} was advanced that the vagi control the permeability of the lung structures and vessels.

Two cases of fatal poisoning with physostigmine have been culled from the literature of the past 16 years, to wit:

1. The day after herniorrhaphy, a patient received an injection, by mistake, of 100 mg. physostigmine (for veterinary use) in an attempt to stimulate bowel movement. He died of pulmonary edema within 30 minutes.¹⁶
2. A 19 year old girl complained of pains in her kidney region which were diagnosed as of sympathicotonic origin. A subsequent injection of physostigmine 1.2 mg. was followed by death in 15 minutes from pulmonary edema. At autopsy, all organs were found to be normal except the lungs; they were filled with serosanguineous fluid.¹⁷

It is notable that the dose of physostigmine used in the latter case is well within the limits of the therapeutic range. Non-fatal cases may not have been brought to public attention. Dr. J. Wilder, in an unpublished communication, mentions that he saw a case of myasthenia gravis which developed pulmonary edema while under intensive treatment with prostigmine.

In both our cases presented here, attacks of pulmonary edema followed immediately upon the administration of enemas. Since the lower and middle hemorrhoidal veins empty into the inferior vena cava, two quarts of fluid in the one case certainly may have tended to flood the lungs when absorbed rapidly. Much more controversial is the relationship of the oil retention enema in case 2 to the development of pulmonary edema. However, there are reports⁴ that rapid distention of hollow viscera may be a factor in causing pulmonary edema, perhaps representing thus a kind of additional parasympathetic stimulus. An effect of such distention on the coronary circulation has been described.¹⁸

Prostigmine has an effect on voluntary muscle⁷ apart from its nicotinic and muscarinic actions. It is this action on the neuromuscular junction which determines its therapeutic use in neurological conditions, e.g., myasthenia gravis, parkinsonism, multiple sclerosis, etc. This particular therapeutic effect of prostigmine on muscles is blocked by curare and by quinine, but not by atropine. It is therefore suggested that prostigmine be combined with atropine to avoid any untoward effects of the muscarinic action of prostigmine.

SUMMARY

Two cases of multiple sclerosis are reported in which attacks of pulmonary edema with recovery were observed during treatment with prostigmine immediately following enemas. The various factors which may have contributed to the development of pulmonary edema in these cases have been discussed, and the relative importance of the treatment with prostigmine noted. It is suggested that prostigmine be combined with atropine to avoid untoward side effects.

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LIPOID GRANULOMATOSIS (XANTHOMATOSIS) WITH MARKED PULMONARY FIBROSIS AND COR PUL- MONALE AS OUTSTANDING MANIFESTATIONS*

By SAMUEL J. SCHNEIERSON, M.D., F.A.C.P., and LOUIS SCHNEIDER, M.D.,
New York, N. Y.

LARGELY as a result of the contributions of Hand,¹ Schüller,² and Christian,³ "xanthomatosis" of the skeletal type became clearly established as a disease found principally in children. The clinical manifestations of the peculiar pathological process were described as defects in membranous bones, exophthalmos and diabetes insipidus, and were all attributable to "xanthomatous" involvement of membranous bones (chiefly skull) and of the hypothalamus. Since these early case

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From Lebanon Hospital and The Bureau of Tuberculosis, Dept. of Health, New York City.

reports, the same pathological process has been found in other patients, not a few of them adults. It seems obvious now that the earlier cases with skull defects, exophthalmos and diabetes insipidus represented merely the first recognized instances of a peculiar lipid granulomatosis (or xanthomatosis),^{4, 5} and that the symptomatology of the disease depends entirely on the location, number, and size of the lesions. Thus, many bones other than the skull, including long bones, have not infrequently been involved and, likewise, the skin, lymph glands, and many other organs have been implicated in various cases.

The diagnosis of lipid granulomatosis in the absence of the Hand, Schüller-Christian triad (defects of membranous bones, exophthalmos and diabetes insipidus) has not received much attention. Only a few cases so diagnosed have been reported.⁴

Regardless of the causative factor or factors of the disease, concerning which there is difference of opinion, certainly the reticulo-endothelial system is outstandingly involved. Wherever there is reticulo-endothelial tissue there may conceivably be found the characteristic pathological lesion of the disease. There is unanimity of opinion in respect to involvement of the reticulo-endothelial system among workers who otherwise have different views as to the pathological physiology.

Pulmonary infiltration has been observed by a number of authors.^{6, 7, 8, 9, 10} Most often it proves to be an incidental finding discovered in the course of chest roentgen-ray, in a patient with other symptomatic manifestations of the disease. Pulmonary infiltration extensive enough to result in congestive right heart failure (as in the following case) is distinctly rare. We have encountered no case in the literature in which symptoms in an adult patient were exclusively referable to pulmonary involvement and resultant right heart failure. There are pathologists of wide experience who have not seen this pulmonary cardiac combination in their postmortem material of lipid granulomatosis (xanthomatosis).¹¹ Of interest in our case also is the fact that in a preemployment chest roentgenogram at least two years before symptoms of the disease appeared, there was evidence of extensive pulmonary infiltration.

CASE REPORT

The patient, a married white male, an American of Scotch-Irish ancestry, age 35, consulted one of us on July 8, 1946, because of general weakness and progressively increasing shortness of breath on effort. In August, 1940, he had been examined by us for a slight cough and hoarseness of six days' duration. Further inquiry at that time revealed that there was recent slight dyspnea on effort, but this in no wise interfered with the patient's ordinary social or occupational activities. In March, 1938, prior to employment by the New York City Health Department, a routine chest roentgen-ray was taken, the subject being completely free of symptoms. The film (figure 1) disclosed uniformly fuzzy, bilateral symmetrical infiltrations throughout both lung fields, as well as hilar thickening.

Physical examination on August 11, 1940, had revealed a well-nourished, healthy-looking young male adult, age 29 years, whose only positive findings were scattered medium-sized rhonchi at both lung bases. A roentgenogram of the chest revealed a mottling throughout both lung fields which differed little from that in the chest film of March, 1938. Cardiac configuration and size were normal. Sputum examinations were repeatedly negative for tubercle bacilli, and blood Wassermann test, blood count, sedimentation rate and urine examination revealed no abnormalities. The diagnosis

of pneumoconiosis could not be entertained inasmuch as no history of employment in a dusty trade was elicited. Likewise, studies with respect to possible fungus etiology were negative. The clinical impression at that time was that of diffuse pulmonary fibrosis, but admittedly no etiological factor was ascertainable.

Cough and hoarseness cleared up entirely approximately one week after onset, and in all likelihood resulted from an intercurrent respiratory tract infection. The patient was studied again in June, 1941, at which time the slight dyspnea on moderate effort, physical and roentgen-ray findings, were precisely as in August, 1940.

Owing to our absence from civilian practice during the war years, the patient was not seen again until July 8, 1946. His general condition had progressively

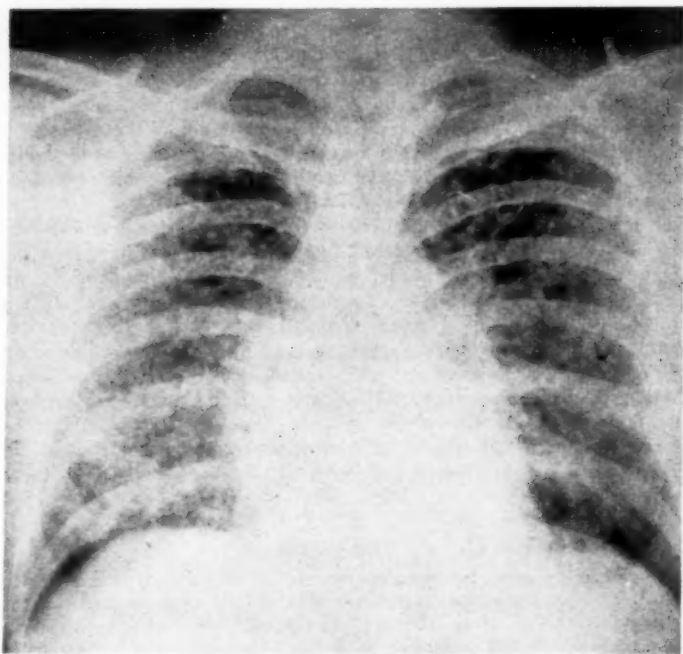


FIG. 1. Preemployment chest roentgen-ray. Patient asymptomatic. Extensive pulmonary infiltration and hilar thickening. Heart not enlarged.

deteriorated since 1941. There was now marked general asthenia, loss of weight from 141.5 lbs. (in August, 1940) to 126 lbs., and marked dyspnea after slight physical effort. This symptom had made it necessary for the patient to quit his occupation as a foreman in an electrical wire factory.

Family history revealed no pertinent data. Past history disclosed only that the patient had had measles in childhood. Reference has already been made to the pre-employment roentgen-ray film taken of this patient's chest in March, 1938.

Physical examination now revealed a malnourished, chronically ill male, appearing older than his actual age of 35. There was slight cyanosis of the lips and cheeks

Dyspnea was marked even at rest, and accentuated by recumbency. Pulse was regular and 112 per minute. There was no exophthalmos. Palpation of the scalp revealed, in the right parietal region, a slightly tender, irregular area of depression of the osseous vault, approximately constituting a quadrilateral area, 8 cm. by 5 cm. At this juncture in the examination the patient volunteered the information that this area of the scalp had been slightly tender for approximately a year. There was no cervical or other adenopathy, nor was there thyroid enlargement. Neck veins were definitely engorged. Chest examination revealed slight dullness over the entire lung area.

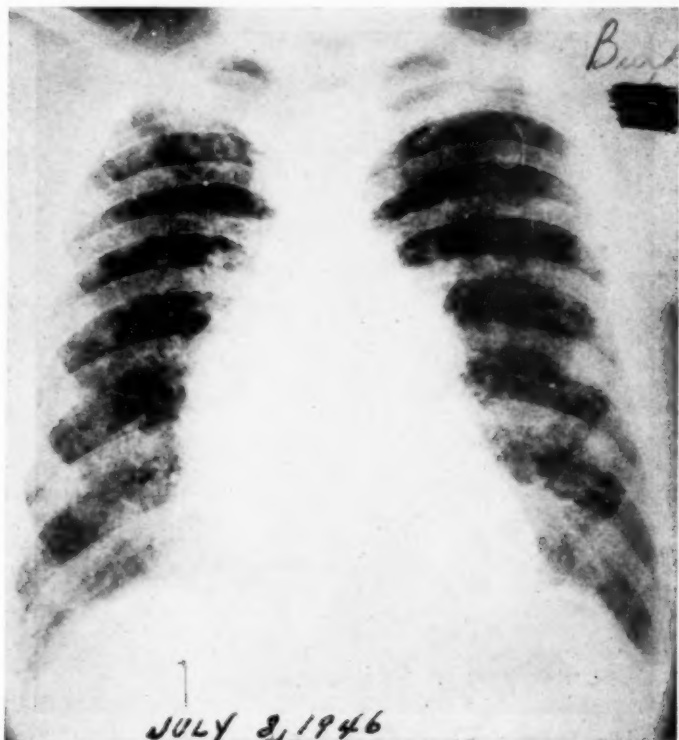


FIG. 2. Illustrates extensive pulmonary fibrosis and definite cardiac enlargement.

somewhat more marked over both lower lobes. Small-sized rhonchi were audible on inspiration and expiration over the entire lung area, but over both lower lobes the rhonchi were louder and more sustained. The heart was enlarged both to the right and left, the maximum apex impulse being palpable 1.5 cm. outside the midclavicular line in the fifth intercostal space. There was sinus tachycardia of 112 per minute and all heart sounds were of poor quality. Abdominal examination revealed the liver to be uniformly enlarged, firm, and slightly tender, its lower edge palpable at the level of the umbilicus. There was slight bilateral, pretibial edema.

Radiographic examination of the chest (figure 2) revealed an extensive interstitial fibrosis throughout both lungs from apex to base. The heart was moderately enlarged, with definite prominence of the pulmonic conus and enlargement of the left ventricle and right ventricle. A roentgenogram of the skull (figure 3) disclosed a large, irregular, "geographic," quadrilateral area of bone destruction in the right parietal region, approximately 8 by 4 cm. in extent.

With these findings it seemed quite clear that the patient was suffering from an advanced degree of diffuse pulmonary fibrosis with resulting chronic cor pulmonale. The presence of an extensive osseous lesion in the skull made it seem likely that the



FIG. 3. Extensive geographic skull defect, right parietal region.

pulmonary findings were not merely those of an isolated pulmonary disease, but rather an incident in the course of a widespread pathological process affecting at least bone and lung. The general appearance of the skull lesion suggested the possibility of lipoid granulomatosis.

Further laboratory and radiographic data were as follows: Urine, faint trace of albumin; repeatedly negative for Bence-Jones protein. Blood Wassermann test negative; hemoglobin 17.05 grams, red blood cells 5,190,000; neutrophils 69 per cent; lymphocytes 28 per cent; mononuclears 1 per cent; bands 2 per cent; blood sugar 93 mg. per cent; non-protein nitrogen 32 mg. per cent; serum albumin 5 per cent; serum

globulin 2.2 per cent; phosphorus 7.4 mg. per cent; total cholesterol 237 mg. per cent; cholesterol esters 91 mg. per cent; alkaline phosphatase 3.3 KA units; acid phosphatase 0.8 KA units; calcium 8.6 mg. per cent; lecithin 140 mg. per cent.

Radiographic examination of the upper two-thirds of right femur disclosed several small cystic areas of bone destruction in the shaft with thickening of the cortex along the upper third. Roentgen-ray study of the left hip and upper two-thirds of the left femur disclosed cystic areas of bone destruction in the descending ramus of the left pubic bone. There was thickening of the cortex of the middle third of the shaft

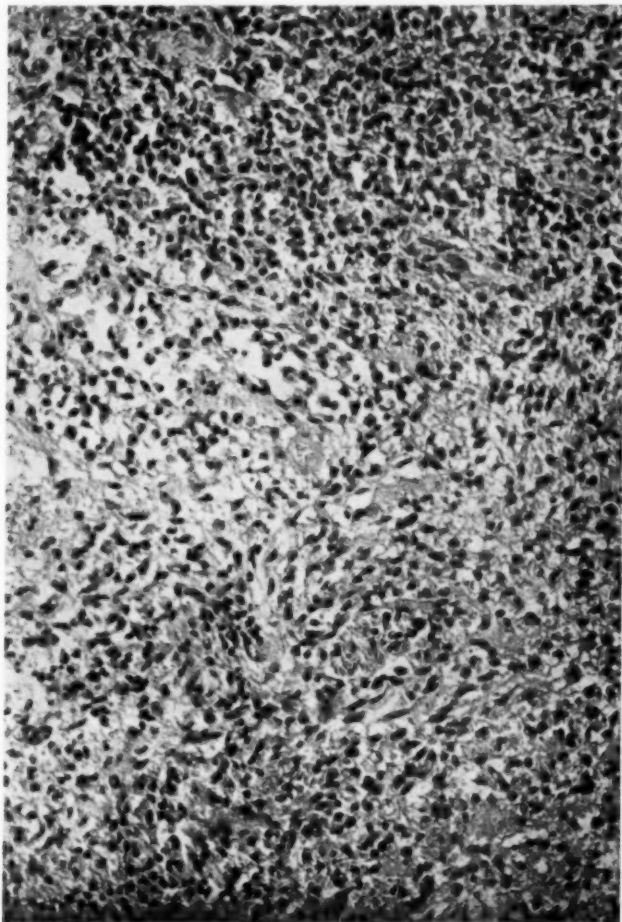


Fig. 4. Microscopic section illustrating histiocytes, foam cells, and other characteristics described in text.

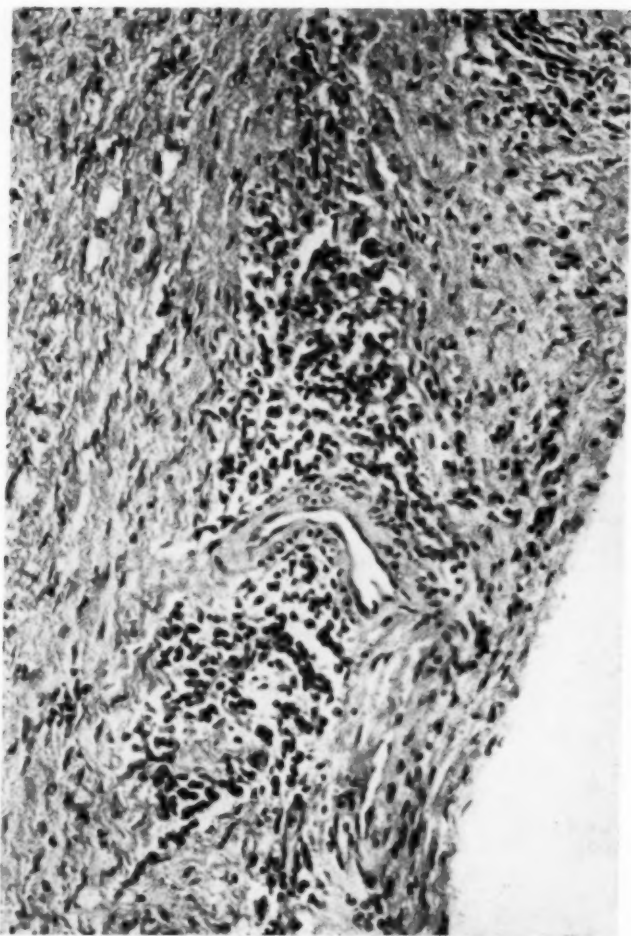


FIG. 5. Illustrates dural attachment to lesion.

of the left femur along the medial aspect. A few linear areas of bone destruction were noted in the cortex. Other skeletal roentgen-rays were negative. An electrocardiogram disclosed evidences of right ventricular strain.

On August 29, 1946, a biopsy of the lesion of the right parietal bone was performed at Lebanon Hospital, New York City. This was reported as follows by Dr. Joseph C. Ehrlich and Dr. H. Cohen (figure 4). *Gross Specimen:* Received four small pieces of tissue. One measures 7 by 4 by 2 mm. and has a solid consistency. One-half of it is uniformly brown-gray in color and the other half is dark yellow with little light yellow nodules within it. Two other specimens are small fragments, solid,



FIG. 6. Pulmonary infiltrations less marked after roentgen therapy. Cardiac enlargement increasing.

and yellowish in appearance. One is somewhat firm and seems to have a layer of dura on it. The fourth piece is a small piece of tissue with a calcified spicule at one edge. Received also another small piece of tissue 6 mm. long taken from the same area for frozen section.

Histopathologic Findings. The fragments of tissue are composed of the following elements: (1) sheets of medium-sized stellate histiocytic cells with finely granular cytoplasm in which, occasionally, finely granular pale brown pigment is present. These cells are sometimes multinucleated; (2) numerous eosinophilic leukocytes, lymphocytes, and moderate numbers of neutrophilic leukocytes and plasma cells; (3) moderate numbers of thin-walled congested blood vessels; occasional large fresh extravasations of erythrocytes; (4) relatively acellular dense fibrous tissue; and (5) a tiny fragment of bone whose trabecular architecture appears essentially normal.

The fragment of tissue available for frozen section consists essentially of fibrous connective tissue and inflammatory cellular elements but relatively few histiocytes. It is probably derived from the dura. Sections of this fragment were examined in polarized light and also after staining by Sudan IV. Numerous tiny doubly refractive crystals and moderate amounts of tiny Sudanophilic droplets were found. Both the doubly refractive crystals and the Sudanophilic droplets were dispersed throughout this tissue along collagen fibers and in vascular septa.

One small zone of necrosis is present. A number of large foam cells in this area may be of simple reactive origin.

The general histopathologic pattern of this granuloma is consistent with the diagnosis of Schüller-Christian disease.

Diagnosis. Lipoid granuloma of skull (of the type seen in Schüller-Christian disease).

In spite of low salt diet, fluid limitation, and digitalis administration, all the symptoms in this patient have progressed strikingly. Beginning October 3, 1946, the patient was given deep roentgen-ray treatment to the anterior and posterior chest fields, at five-day intervals, a total of 800 r, 200 K. V. through $\frac{1}{2}$ cu. and 2 al. filter.

On December 27, 1946, because of increasing enlargement of the liver, with abdominal fullness and markedly increased pretibial edema, intravenous mercurial therapy was instituted twice weekly, in 2 c.c. doses. This has failed to control the increasing peripheral edema and hepatic enlargement. On January 21, 1947 (figure 6), a chest roentgen-ray film disclosed increased cardiac enlargement. The pulmonary infiltration, while still pronounced, appeared less marked than that of July 8, 1946, probably the result of roentgen therapy. In spite of the treatment already detailed, examination of February 25, 1947, reveals marked orthopnea and increased size of the liver, as well as increased peripheral edema.

COMMENT

The finding of notable pulmonary fibrosis in a pre-employment chest roentgen-ray, when this patient was otherwise well, is, we believe, of clinical interest. During the course of chest roentgen-ray surveys conducted among presumably well persons, with the intent of detecting early tuberculosis, the presence of so-called pulmonary fibrosis is not infrequently discovered. Confronted with such an instance, the clinician embarks on a search for etiological factors. Usually the possibility of lipoid granulomatosis is not considered. It now seems to us that in any instance of otherwise unexplained pulmonary fibrosis, especially in children or young adults, this entity must be kept in mind. Further interrogation of the patient and bone roentgen-rays, especially of the skull, may conceivably add other cases similar to ours. Perhaps if complete investigation fails to reveal an etiological factor for pulmonary fibrosis, lung puncture is justified for biopsy. Possibly in our case such a diagnostic measure might have led to an earlier diagnosis than was made. So far as we know, lung puncture has not been given serious consideration in the diagnosis of lipoid granulomatosis.

Early diagnosis is not merely an academic consideration. While reports of treatment by irradiation of osseous lesions in this disease have been commented on favorably by various authors, accounts of treatment of pulmonary lesions by x-ray are rare. Currens and Popp¹² reported a definitely favorable therapeutic response in their case. Imiler¹³ states that roentgen therapy in moderate doses causes a definite therapeutic response. Early treatment when the pulmonary infiltration is predominantly granulomatous may be expected to be of greater effectiveness than that administered when fibrous tissue predominates, a change which is part of the evolution of this disease and one that is likely to render irradiation fruitless.

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**SIMULTANEOUS ASSOCIATION OF SITUS INVERSUS,
CORONARY HEART DISEASE AND HIATUS HERNIA:
REPORT OF A CASE AND REVIEW OF
LITERATURE***

By HENRY N. ROSENBERG, M.D., and I. N. ROSENBERG, M.D.,
Boston, Massachusetts

CONGENITAL dextrocardia with situs inversus is an infrequent but not a rare condition, estimates as to its incidence varying from one in approximately 35,000 individuals¹ to one in 6 to 10,000.^{2, 3, 4, 5} The association of congenital dextrocardia with coronary heart disease is, however, quite rare,^{6, 7} only five such case reports appearing in the literature. No case of hiatus hernia occurring with situs inversus has yet been reported. For this reason it was felt that the report of the following case presenting the coexistence of situs inversus, coronary heart disease and hiatus hernia would be of interest.

CASE REPORT

The patient, a 54 year old Armenian-born, retired storekeeper, consulted one of us (H. R.) with a chief complaint of recurrent pain in the chest of approximately five years' duration. He had enjoyed good health until five years ago, when following a mild illness of one week's duration marked by cough, he noticed the onset of episodes of pain in the upper anterior chest just to the right of the sternum. At that time he was seen at a community hospital where, after roentgen-ray examination, he was told "there was something wrong in his chest." Two years before, because of progression of his symptoms, he was seen at a large clinic, where he was informed that he had

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From the Fifth (Boston University) Medical Service, Boston City Hospital, and Department of Medicine, Boston University School of Medicine.

heart disease. Nitroglycerine was prescribed, which effectively and rapidly relieved the pain. During the past two years, however, the attacks had increased in frequency and severity, necessitating his retirement from business and reducing him to a semi-invalid status. Mild exertion or emotion of moderate intensity precipitated the episodes of pain, which was described as a sensation of pressure or constriction in the upper chest to the right of the sternum. The pain radiated to the shoulders and down both upper extremities, apparently equally, and was associated with numbness

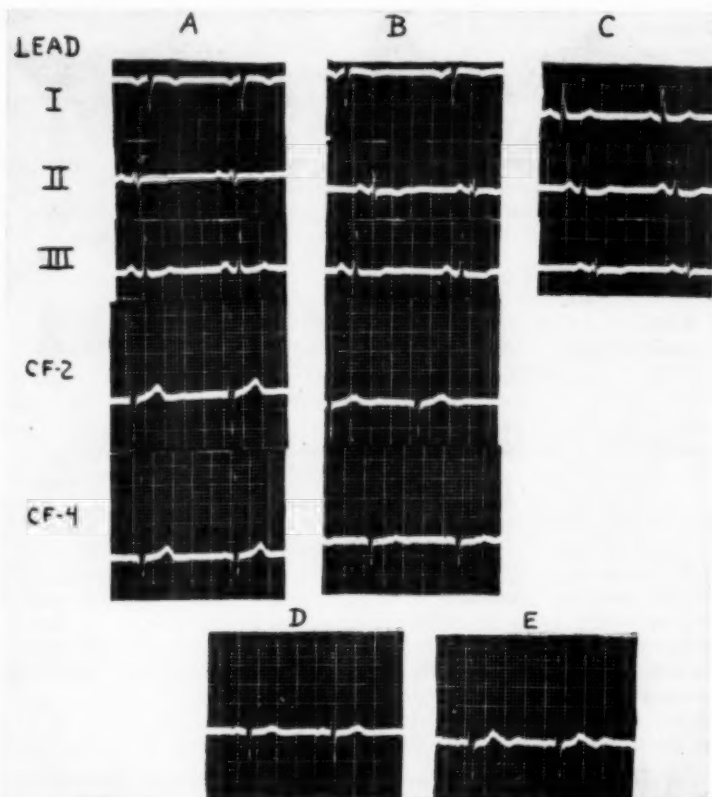


FIG. 1. Column A represents EKG tracings at rest. In Column B are the tracings obtained during the recovery phase (10 minutes) following 20 trips on the 2 step staircase; the amplitude of the T-waves in each lead is diminished, as compared with A, and T_2 (equivalent to T_1 in sinistocardia) has become diphasic. Column C shows the resting electrocardiographic limb leads "corrected for dextrocardia" by reversal of the arm electrodes. D is the tracing (CF, obtained with the patient standing) immediately prior to the exercise tolerance test; E is the corresponding tracing immediately following completion of the test, at the time of anginal pain. The increased amplitude of T is striking.

In all fourth lead tracings the correction for dextrocardia has been made, the chest electrode being placed on the right chest, its position and nomenclature corresponding to those employed when the precordium is on the left.⁴²

in the forearms and hands. In addition to exercise, which constantly induced an attack of pain, the ingestion of a heavy meal was often followed by chest pain subjectively indistinguishable from that associated with exertion and also relieved by nitroglycerine. Attacks were frequently nocturnal, waking him from sleep; he had discovered empirically that abstaining from all food after 5 or 6 p.m. and sleeping in a semi-recumbent position were measures which diminished the frequency of these nocturnal episodes. There had been no abdominal pain, dysphagia, nausea, vomiting, or excessive belching; no dyspnea, orthopnea, chronic cough or swelling of the ankles. At the time of examination he was taking 8 to 10 tablets of nitroglycerine daily.

The past history was non-contributory. The family history revealed that a brother had died of myocardial infarction at the age of 42; there was no history of congenital abnormalities in other members of the family, or of consanguineous marriage.

Physical examination: Temperature 98.0° F., pulse rate 70 per minute, respiratory rate 20. The head and neck were normal; the fundi revealed no evidence of arteriosclerosis. The chest was somewhat emphysematous. The cardiac apex impulse was palpable in the fifth right interspace in the mid-clavicular line; there was no evidence of cardiac enlargement to percussion. A grade 2 apical, non-transmitted systolic murmur was audible. The blood pressure was 130 mm. of mercury systolic and 84 mm. diastolic. The abdomen revealed no masses, tenderness or spasm; hepatic dullness extended down to the left costal margin. The right testicle was lower than the left. The extremities were normal. Neurological examination revealed no abnormalities. The patient had always been right handed.

Laboratory studies: Hemoglobin (Sahli) was 94 per cent, the red blood cell count 4.9 million per cubic millimeter, the white blood cell count 7,500 with a normal differential. The Hinton test was negative. Urine examination was negative. Guaiac tests on the stool on several occasions revealed no occult blood. Roentgen-ray of the chest confirmed the clinical impression of dextrocardia. The heart was of normal size and shape; the aortic knob was somewhat prominent. The lung fields were normal, and there was no evidence of bronchiectasis. Electrocardiogram (figure 1) revealed the changes typical of congenital mirror-image dextrocardia; all complexes of Lead I were inverted, and Leads II and III were transposed as compared with records of individuals in whom the organs are more conventionally disposed. (For comparison, the electrocardiographic records obtained from the patient by reversing the arm electrodes are also shown in figure 1 C.) The low voltage of the T-waves in all leads and the diphasic T₁ (corresponding to the conventional T₂) are suggestive of myocardial disease.

A gastrointestinal series revealed a small hiatus hernia (figure 2), a portion of the cardiac part of the stomach being visible above the diaphragm adjacent to the esophagus. The shadow of the liver was visualized in the left upper quadrant, that of the spleen in the right upper quadrant of the abdomen.

Aminophylline, 3 grains orally four times a day was prescribed, but it did not effect appreciable change in the symptomatology, nor diminish the need for nitroglycerine. However, when syntropan, 100 mg. thrice daily was given, some diminution in the severity of the attacks ensued. The further addition of 20 drops of tincture of belladonna q.i.d. to the therapeutic regimen practically eliminated the nocturnal attacks and reduced the diurnal episodes to three or four per day.

DISCUSSION

It has been stressed repeatedly in recent years that hiatus hernia may be responsible for episodes of chest pain very closely simulating angina pectoris associated with coronary heart disease.^{8, 9, 10, 11, 12, 13, 14, 15} In an attempt to

evaluate more clearly and objectively what part of the symptomatology in this case was of cardiac origin, it was deemed advisable to test coronary sufficiency. A safe and reliable¹⁶ estimate of the adequacy of the coronary circulation is obtained by the exercise tolerance test, in which the subject performs a certain amount of work, and observation is made of both the onset of anginal pain and change in the electrocardiographic pattern immediately before and after exercise.¹⁷ It was found on several tests on different occasions in the patient under discussion that after approximately 20 trips on the two-step staircase, chest pain identical with that characterizing the patient's illness occurred; and the electrocardiogram



FIG. 2. Appearance of hernia following ingestion of barium meal (arrows).

immediately following the exercise showed significant changes from the pattern prior to exertion; figure 1E illustrates the rise in amplitude of T_4 occasioned by exercise. Riseman and his colleagues¹⁷ have pointed out that Lead IV more regularly than the limb leads shows these changes during and after angina; they observed that although both normal individuals and those with angina pectoris may show T-wave depression following exercise, increased amplitude of T_4 was noted only in the latter. It has been observed that in the chest pain associated with hiatus hernia, unlike that of angina pectoris due to coronary heart disease, there is no constant relationship between exertion and the induction of pain.^{8, 12} In our patient such a constant relationship did exist, both from the clinical history

and from the observation of the exercise tolerance tests, in which pain always followed the performance of approximately the same amount of work.

In summary, from the character of the pain and its radiation, from the constancy of the relation between exertion and pain, from the response to nitroglycerine, from the electrocardiographic suggestion of myocardial disease, and from the characteristic electrocardiographic changes in the exercise tolerance test, the diagnosis of coronary heart disease with angina pectoris seems firmly established. The contribution of the hiatus hernia to the symptomatology is difficult to evaluate precisely, but the following considerations indicate that a component of the pain was due to this condition: (a) chest pain occurring at rest was invariably nocturnal, occurred in recumbency, and could be largely prevented by the eating of small meals and by assuming an upright posture; the relationship of the pain due to the hiatus hernia to the ingestion of food and the influence of position upon it are well known^{12, 13}; (b) the administration of syntropan and belladonna, agents which are ineffective in the treatment of the pain of coronary heart disease¹⁸ but often effective in hiatus hernia, caused reduction in the severity and frequency of the nocturnal attacks but was without influence on the attacks of pain precipitated by exercise, which were promptly relieved by nitroglycerine. It seems clear that this patient therefore presents congenital dextrocardia with situs inversus on roentgenological evidence, coronary heart disease with angina pectoris on the basis of the clinical and electrocardiographic findings, and symptomatic hiatus hernia, demonstrated by roentgen-ray, the clinical history and the favorable response to antispasmodics and diet.

COMMENT

The rarity of acquired organic heart disease in individuals presenting dextrocardia with situs inversus has been noted by several observers^{6, 7, 19, 20}; the infrequency of the association is even more striking when it is seen that situs inversus itself is apparently more common than is generally realized, the incidence in the general population being approximately one in ten thousand. In table I we have compiled from the literature some of the figures on the frequency of congenital dextrocardia. The rarity of the association of acquired heart disease with situs inversus is in marked contrast with the positive correlations existing between situs inversus and congenital abnormalities (in addition to the dextrocardia) of the cardiovascular and other systems^{21, 22} and especially between bronchiectasis and sinusitis with situs inversus, the respiratory tract pathology having been found in approximately 20 per cent of the cases of transposition.^{4, 22, 23, 24} It has been suggested that situs inversus may be caused by one of two mechanisms: one form is genetically determined and carries with it no liability (the concept that situs inversus is inherited as a Mendelian recessive character finds statistical support in Cockayne's studies²¹); the other form is the result of maldevelopment on the basis of an unfavorable intrauterine environment, under which conditions other congenital abnormalities might occur in addition to visceral transposition.⁴

We have been able to find in the literature a total of 15 cases of acquired heart disease associated with congenital dextrocardia and situs inversus. These include: rheumatic heart disease, three cases (one case of mitral stenosis²⁵ and two cases of combined mitral and aortic lesions^{26, 19}); two cases of syphilitic

aortitis^{24, 27}; and one case of calcareous aortic stenosis²⁰; one case of chronic cor pulmonale²⁸; one case which from the clinical evidence presented is strongly suggestive of thyrotoxic heart disease, although no etiologic diagnosis is made in the case report²⁹; two cases of hypertensive heart disease^{30, 31}; one case of combined hypertensive and coronary heart disease⁷; and four cases of coronary heart disease.^{32, 33, 3, 6} In five of the 15 cases symptoms of angina pectoris or myocardial infarction were present; in three of the cases the pain was in the right chest or radiated only to the right arm^{6, 24, 33}; in one case⁷ it was in the left chest, and

TABLE I
Incidence of Congenital Dextrocardia

Number of Cases of Congenital Dextrocardia Found	Number of Individuals Examined	Nature of Examination	Incidence Frequency	%	Author
		Military service (physical examination)	1:35,000	.0029	LeWald ¹
14	124,830	Autopsy (consecutive)	1:8920	.011	German autopsy records, cited by Cockayne ²¹
23	232,112	Consecutive hospital patients	1:10,090	.0099	Adams and Churchill ⁴
15	180,000	Military service (x-ray)	1:12,000	.0083	Geeslin and Tyler ³
8	100,000	Military service (x-ray)	1:12,500	.0080	Caplan ²
36	223,182	Military service (x-ray)	1:6200	.016	Morse ⁵
6	36,717	Mass x-ray survey	1:6120	.016	Russakoff and Katz ⁴¹
40	442,252	Mass x-ray survey	1:11,060	.0091	Gould ⁴²
6	37,257	Mass x-ray survey	1:6210	.016	Robins and Ehrlich ⁴⁴
Total 148	1,376,350		1:9300	.0108	

In several instances above, a clear-cut distinction between the two forms of congenital dextrocardia, namely isolated dextrocardia and that occurring as part of a general visceral transposition, has not been made. Since, however, the former anomaly is much rarer than the latter^{45, 46, 47}, the incidence of situs inversus is probably not significantly lower than the average figure derived from the total.

in the remaining case⁸ the pain was in mid-chest and radiated to both arms. In our patient the pain was in the right chest and radiated to both arms. It is apparent from the five cases in the literature and from the case reported above, that in congenital dextrocardia the pain associated with myocardial anoxia tends to be referred to the side of the body on which the organ is situated; but this is not invariable as indeed is the case in sinistocardia, where anginal radiation tends to be to the left, but may be to both sides, or only to the right.³⁴ King²⁴ discussing reference of pain in cases of visceral transposition suggests that con-

tralateral reference may be a result of the failure of the nervous pathways to share in the general visceral rotation.

We have been unable to find a case report in the literature of hiatus hernia in association with congenital dextrocardia and situs inversus. Acquired dextrocardia caused by displacement of a previously normally situated heart by the presence of abdominal viscera in the left chest as a result of a diaphragmatic hernia is not uncommon; indeed, since diaphragmatic hernia occurs much more commonly on the left than on the right, the condition is one of the common causes of acquired dextrocardia.³⁵

In the past decade increased recognition has been accorded to the fact that hiatus hernia may produce chest pain very similar to the anginal syndrome associated with coronary heart disease.^{8, 9, 12, 36} Since symptoms associated with hiatus hernia tend to occur in those age groups in which coronary and hypertensive heart disease show their highest frequency the lesions frequently coexist; in Jones' ¹² series of 128 cases of hiatus hernia there were 13 individuals who also had heart disease, while Ohler and Ritvo ¹³ found probable heart disease in six of their 104 cases. There can be no doubt that many hernias are asymptomatic and are detected as incidental findings in a gastrointestinal series.^{13, 37, 38} On the other hand, it is true that in many cases of heart disease with angina pectoris there are no significant resting electrocardiographic abnormalities³⁹ nor other obvious objective manifestations of the disorder. In a case of chest pain in which a hiatus hernia is demonstrated, the possibility that coronary heart disease is present should always be considered. As Moschowitz ⁴⁰ pointed out, precise diagnosis and definitive treatment demand a differentiation of the cause of the pain and ascribing it to one or the other cause or possibly both. Much has been written emphasizing the error of making a diagnosis of coronary heart disease in cases where the symptomatology is actually due to hiatus hernia^{8, 14, 40}; however, the possibility of overlooking a true angina pectoris in the presence of an asymptomatic hiatus hernia has not been equally stressed. From careful clinical appraisal of the symptomatology, electrocardiograms, roentgen-ray, the response to treatment with parasympatholytic or antispasmodic drugs, bland diet and coronary vasodilators, in most cases a precise diagnosis may be made, with evaluation of the contribution of each lesion to the symptoms.

SUMMARY

1. An unusual case of congenital dextrocardia with situs inversus associated with coronary heart disease, angina pectoris and hiatus hernia is presented. This is the first such case to be reported.
2. The literature relating to the incidence of congenital dextrocardia is reviewed. The anomaly has an incidence of about 0.01 per cent.
3. Case reports in the literature on situs inversus associated with acquired heart disease are reviewed.
4. The need for careful differentiation of coronary heart disease from hiatus hernia as a cause of chest pain is emphasized.

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ELECTROCARDIOGRAPHIC EVIDENCE OF RIGHT AND LEFT ANTERIOR WALL INJURY DUE TO GUNSHOT WOUND OF THE HEART *

By L. KAPP, M.D., and A. GRISHMAN, M.D., *New York, N. Y.*

SINCE gunshot and stab wounds of the heart produce localized myocardial lesions, they are of considerable clinical importance in the interpretation of electrocardiographic changes. No other myocardial disease demonstrates localization so well, and similar lesions can be produced only by direct, localized experimental injuries of the myocardium in animals. In both gunshot and stab wounds, during the first two weeks, the electrocardiogram shows predominantly

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From the Cardiac Section of the Medical Service of the Veterans Hospital, Bronx, New York.

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changes associated with pericarditis. There have been few case reports with permanent electrocardiographic evidence of injury of the right or left ventricle.¹

Cases with electrocardiographic evidence of post-traumatic left anterior wall infarction or injury are usually the result of laceration, severance, or operative

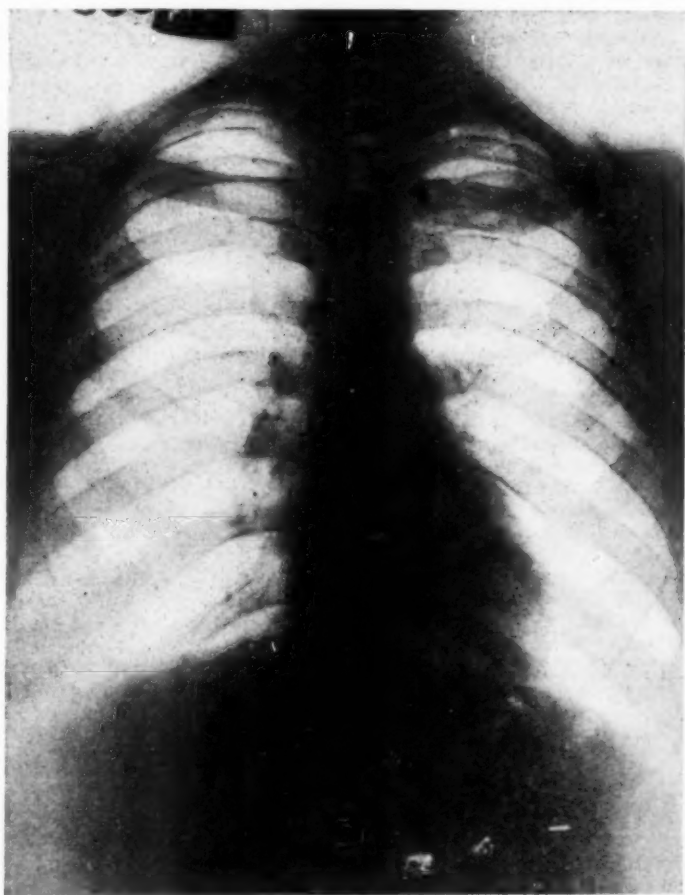


FIG. 1. Roentgenogram, posterior-anterior view: A metallic fragment is seen at the border between right and left ventricle below the level of the aortic valve.

ligation of the anterior descending branch of the left coronary artery. Q-waves and T-wave inversions are found in Leads I and IV. Cases of right ventricular injury often develop transient or permanent right bundle-branch block.² T-wave changes and occasionally small Q-waves have been present in Leads II and III

or in all three leads.^{1,2} No definite electrocardiographic pattern of right ventricular injury has been established in human beings, since isolated myocardial infarction of this region never occurs.

The following case of gunshot wound of the heart is presented because of the



FIG. 2. Left lateral view: The projectile is seen to be anteriorly within the myocardium.

characteristic electrocardiographic findings which made it possible to localize the injury to the anterior wall of the right and left ventricle. This interpretation was corroborated by the roentgenological localization of the shrapnel fragment which caused the injury.

CASE REPORT

A 23 year old World War II veteran was referred to the Cardiac Section of the Veterans Hospital, Bronx, New York, for consultation. While on active duty in Belgium as a gunner with an anti-tank outfit, the patient was wounded by a high explosive shell in September, 1944. Numerous shrapnel fragments penetrated deeply into the soft tissues of his left leg, hand, arm, neck, face, and chest. At no time did he lose consciousness, although he bled profusely. An operation was performed in a field hospital, where one fragment was removed from the pericardium through an anterior chest wound to the left of the sternum. Another fragment was seen in the myocardium but was not removed. Traveling in an air ambulance from Paris to England nine days later he developed marked dyspnea. He was admitted to a hospital in England and was kept in an oxygen tent for some time with gradual and progressive disappearance of his symptoms. An abscess of the anterior chest wall had formed, and this was incised and drained with complete healing. Roentgen-ray examinations of the chest in October 1944, revealed a moderate left pleural effusion and a metallic foreign body within the anterior wall of the heart, probably in the right ventricle. On fluoroscopy this metal fragment was seen to pulsate vigorously. A contemplated operation for its removal was deferred because of the onset of repeated attacks of severe, stabbing, precordial pain associated with moderate dyspnea on exertion. During the next few months these attacks gradually decreased in frequency. In March, 1945, he was transferred to Valley Forge General Hospital and a few months later to Ashford General Hospital for further evaluation of his cardiac status. He was finally discharged from Walter Reed Hospital. Although surgical removal was considered at various times, it was thought to be more dangerous than the remote possibility that the foreign body would penetrate to the endocardial surface, be embolized, or be the site of bacterial endocarditis. Although cardiac neurosis was regarded as the most likely cause of the paroxysmal angina pectoris and dyspnea, nevertheless its organic origin could not be definitely excluded.

At the present time the patient complains of frequent pain in his numerous scars, particularly in his left hand, where extensive plastic surgery has been done. He often experiences a heavy feeling and tightness in his chest, mild precordial pain, and dyspnea after walking only two flights of stairs. He has had no complaints of cough or expectoration and never developed edema of his lower extremities.

Physical Examination. The patient was well built and nourished, and appeared in no acute distress or discomfort. There were multiple scars due to gunshot wounds and plastic surgery on the left anterior chest, left arm, forearm, wrists, hand and right shoulder. There was one postoperative scar six and one-half inches in length extending from the left sternal margin to the anterior axillary line at the level of the third intercostal space. Cyanosis, edema, and clubbing were not present. The apical impulse was felt within the midclavicular line. No abnormal pulsations or thrills were noted. The heart sounds were of good quality. There were no murmurs or friction rub. Examination of the lungs and abdomen revealed no abnormality. The blood pressure was 130 mm. Hg systolic and 80 mm. diastolic in both arms.

Electrocardiographic Examinations. The conventional electrocardiogram revealed the following: Regular sinus rhythm, tendency to right axis deviation, deep Q-wave, in Leads II, III, CF₁, CF₂, CF₃ and CF₄. The T-waves were inverted in CF₁ and CF₂, low in CF₃ and iso-electric in CF₄.

Augmented unipolar extremity leads revealed a deep Q-wave in aV_F, a slight depression of the ST-segment in aV_L, and inversion of the T-wave in aV_L. Multiple chest leads recorded with a unipolar central terminal revealed deep Q-waves in V₁, V₂, V₃, and small Q-waves in V₄ and V₅. The T-wave was semi-inverted in V₃ and inverted in V₄.

These changes ordinarily would have been interpreted as indicating a previous anterior and posterior wall infarction or injury. Knowing, however, that the myocardial trauma had occurred only anteriorly, they were regarded as diagnostic of right and left anterior wall injury.

Roentgenographic and Fluoroscopic Examination. Radiographic examination of the chest in various positions revealed a metallic fragment 14 by 8 by 6 mm. anteriorly, at the border of the right and left ventricle and somewhat below the level of the aortic valve. Fluoroscopy revealed it to be deep within the myocardium and to pulsate vigorously with cardiac contractions. Several additional metal fragments were seen within the left chest. The left clavicle showed evidence of an old healed fracture.



FIG. 3. Left anterior oblique view: The shrapnel fragment is seen well within the cardiac shadow.

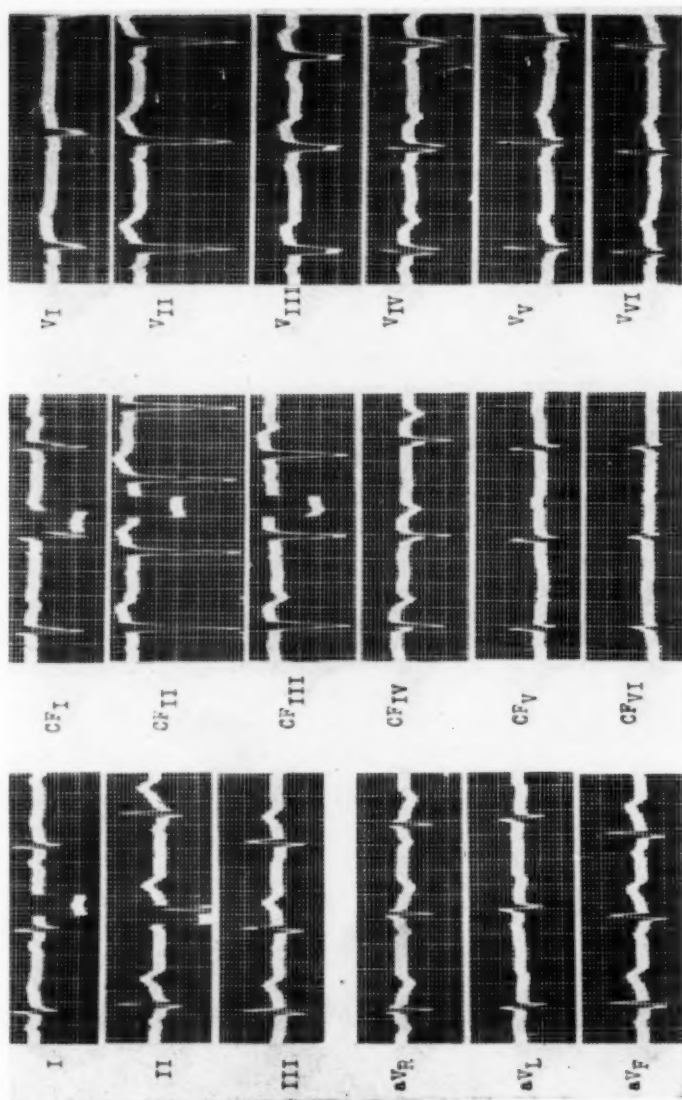


FIG. 4. The electrocardiogram shows evidence of right and left anterior wall injury: Deep Q-waves are present in Leads II and III, CF I-VI, aVR, aVL, and aVF.

COMMENT

Case reports of stab or gunshot wounds of the heart with electrocardiographic evidence of left anterior wall injury have not been rare.² However, in our opinion none has been observed with well defined electrocardiographic evidence of right anterior ventricular wall injury. The myocardial infarction encountered in acute coronary occlusion rarely involves the wall of the right ventricle. Electrocardiographic findings of right ventricular infarction have thus far not been described from clinical observations. In the experimental animal, right ventricular injury of the anterior as well as diaphragmatic surface results in the development of Q-waves, R-ST segment elevations and subsequent T-wave changes similar to those seen in left posterior wall infarction.³ Therefore a deep Q-wave in Leads II and III, elevations of the RST segments in Leads II and III, and T₂ and T₃ inversion are found in left posterior wall infarction as well as right ventricular infarction or injury. In our case no injury of the left posterior surface occurred, as the fragment entered through the anterior chest wall. Pericarditis, pericardial effusion, or adhesions are known not to result in Q-waves. The metallic foreign body as seen roentgenographically gives the exact site of the myocardial injury: anterior surface of the heart involving the left and right anterior wall. Since it is deep within the myocardium, one can reasonably assume that it caused extensive necrosis and subsequently scar tissue. Because of this we feel that the electrocardiographic findings are those of right and left anterior wall injury.

Surgeons who have had considerable war experience with gunshot wounds of the heart are of the opinion that metallic fragments should be removed under all circumstances because of possible complications.^{4,5} Delivery into the ventricular cavity with peripheral embolization may occur at any time, soon after the injury or years later. Aneurysm of the involved ventricle may develop and subacute bacterial endocarditis may occur at the site of the projectile, walled off by connective tissue. Constrictive pericarditis due to an unremoved foreign body from the pericardium has been observed.⁶ Pressure on the cardiac nerve plexus may cause angina pectoris, completely relieved by removal of the projectile.⁷ While the electrocardiogram may be of considerable help in the localization of the cardiac injury in gunshot wounds, its usefulness for operative indication appears limited. The cases reported and our own experience do not allow us to draw any conclusions in this respect. Cases with persistent electrocardiographic findings due to an unremoved shrapnel or projectile may be perfectly asymptomatic, while others with complete electrocardiographic recovery may show signs and symptoms of cardiac embarrassment. Evaluation of the danger involved in removal of the fragment, as against the remote danger of future complications, should be the only guide.⁸

SUMMARY

A case of gunshot wound of the heart involving the right and left anterior ventricular surfaces is presented. The site of the cardiac injury is demonstrated roentgenographically by an unremoved metallic fragment. Electrocardiographic findings characteristic of right and left anterior wall injury are shown in this case. The possible complications due to unremoved foreign body from the heart

are discussed. The limitations of the electrocardiogram as an indication for surgical intervention are briefly indicated.

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EDITORIAL

BIOLOGICAL COMPETITION BETWEEN STRUCTURALLY RELATED COMPOUNDS: CLINICAL IMPLICATIONS

THE introduction in 1935 of the sulfonamide group of drugs¹ opened a new era of chemotherapeutic endeavor. In 1940 the publication of the Woods-Fildes theory² provided not only a satisfactory explanation of the mode of action of these drugs but also a highly important basis for a rational extension of chemotherapeutic research. The basis of the theory was the principle of the biological competition of structurally related compounds. The para-amino benzoic acid-sulfonamide relationship admirably exemplifies this concept.



FIG. 1.

Woods reported that yeast extracts contained a substance which reversed the inhibitory action of sulfanilamide on the growth of hemolytic streptococci. This substance was identified with para-amino benzoic acid and attention was called to the chemical similarity of the drug to this compound (figure 1). Para-amino benzoic acid was considered to be an essential metabolite for hemolytic streptococci, and the effectiveness of sulfanilamide in producing bacteriostasis was thought to be directly related to the structural similarity between the two. Fildes³ had defined an essential metabolite as an organic substance without which metabolism cannot proceed to the extent required by growth. Under normal circumstances of bacterial growth, PABA was utilized by some intracellular enzyme system. It was suggested that the structural analogue (sulfanilamide) competitively displaced the normal metabolite, thereby interfering with some normal enzymic function with resultant bacteriostasis. Subsequently, PABA was recognized as a factor essential for the growth of a number of bacterial species⁴ and was included in the vitamin B complex.

¹ DOMAGK, G.: Ein Beitrag zur Chemotherapie der bakteriellen Infektionen, Deutsch. med. Wchnschr., 1935, lxi, 250.

² WOODS, D. D.: The relation of p-amino benzoic acid to the mechanism of action of sulphanilamide, Brit. Jr. Exper. Path., 1940, xxi, 74.

³ FILDES, P.: The mechanism of the anti-bacterial action of mercury, Brit. Jr. Exper. Path., 1940, xxi, 67.

⁴ RUBBO, S. D., and GILLESPIE, J. M.: Para-amino benzoic acid as a bacterial growth factor, Nature, 1940, cxlvi, 838.

The nature of the cellular metabolic mechanism involved in this competitive reaction was unknown at the time of Woods' studies. The discovery of the structure and synthesis of folic acid in 1946⁵ shed additional light upon this problem. Folic acid was found to consist of para-amino benzoic acid, glutamic acid and the pterin ring. It now seems established beyond reasonable doubt that the sulfonamides prevent the synthesis of folic acid through their interference with the incorporation of para-amino benzoic acid in the folic acid molecule.⁶ Since the latter is essential for the growth of many bacteria, interference with its formation leads to bacteriostasis. Microorganisms which are entirely independent of the need for folic acid are not sensitive to sulfonamides. Bacteria which require ready-made folic acid as a growth factor are also insensitive to the sulfonamides, since they lack the metabolic step upon which the drug acts. On the other hand, sulfonamide-sensitive organisms are those which must form their own folic acid from para-amino benzoic acid. Evidence has recently accumulated which extends our information even somewhat further regarding the rôle of folic acid in cellular metabolism. In a manner not yet elucidated, it appears that folic acid is concerned in intracellular syntheses of amino acids, purines and pyrimidines.⁷

The basic concept of the biological antagonism of structurally related compounds has been subjected to additional investigation, with some very striking results. Wooley and White⁸ fed mice an analogue of thiamine, pyrithiamine and were able to produce signs of a severe thiamine avitaminosis which could be reversed by feeding the vitamin. Signs of scurvy were induced in mice and guinea pigs by the feeding of gluco-ascorbic acid, an analogue of ascorbic acid.⁹ These changes could also be reversed by feeding the vitamin. Pyridoxine deficiency has been induced in chickens by feeding the analogue, desoxypyridoxine.¹⁰ Numerous additional examples could be cited.

It is worth while here to stress briefly a fundamental principle in this competitive phenomenon. The effect of an antagonist is dependent not upon the absolute amount used but rather upon the ratio of the quantity of analogue to that of metabolite.¹¹ This ratio is expressed in terms of a so-

⁵ ANGIER, R. B., BOOTH, J. H., HUTCHINGS, G. L., MOWAT, J. H., SEMB, J., STOKSTAD, E. L. R., SUBBA ROW, Y., WALLER, C. W., COSULICH, D. B., FAHRENBACH, M. J., HULTQUIST, M. E., KUH, E., NORTHEY, E. H., SEEGER, D. R., SICKELS, J. P., and SMITH, J. M.: The structure and synthesis of liver, *L. casei* factor, Science, 1946, ciii, 667.

⁶ LAMPEN, J. O., and JONES, M. J.: Antagonism of sulfonamide inhibition of certain lactobacilli and enterococci by pteroyl-glutamic acid and related compounds, Jr. Biol. Chem., 1946, clxvi, 435.

⁷ LAMPEN, J. O., ROEPKE, R. R., and JONES, M. J.: The replacement of p-amino-benzoic acid in the growth of a mutant strain of *E. coli*, Jr. Biol. Chem., 1946, clxiv, 789.

⁸ WOOLEY, D. W., and WHITE, A. G. C.: Production of thiamine deficiency disease by feeding of a pyridine analogue of thiamin, Jr. Biol. Chem., 1943, 285.

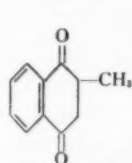
⁹ WOOLEY, D. W., and KRAMPITZ, L. O.: Production of a scurvy-like condition by feeding of a compound structurally related to ascorbic acid, Jr. Exper. Med., 1943, lxxviii, 333.

¹⁰ OTT, W. H.: Antipyridoxine activity of 2, 4-dimethyl-3-hydroxy-5-hydroxymethyl-pyridine in the chick, Proc. Soc. Exper. Biol. and Med., 1946, lxi, 125.

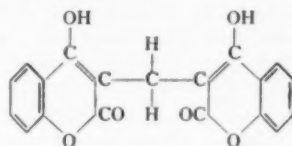
¹¹ WOOLEY, D. W.: Recent advances in the study of biological competition between structurally related compounds, Physiol. Rev., 1947, xxvii, 308.

called inhibition index. The inhibition index is usually greater than one, i.e. proportionately smaller quantities of metabolite are required to reverse the inhibition induced by an analogue. This may be due to a greater natural affinity of the cellular enzyme for the metabolite.

The phenomenon of biological competition of structurally related compounds has many implications. Used as biochemical tools, inhibitory structural analogues, by specifically interfering with a metabolic process, may help to elucidate phases of intermediate metabolism previously unknown. The developments based upon the PABA-sulfonamide antagonism offer an excellent example of this. Furthermore, the utilization of varied analogues of the same metabolite may cast additional light upon varied functions of the latter. The regulation of certain metabolic activities by pairs of normally occurring structural analogues has been postulated. The estrogen-androgen relationship may be mentioned in this connection.¹²



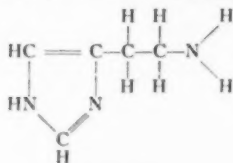
Synthetic Vitamin K (Menadione)



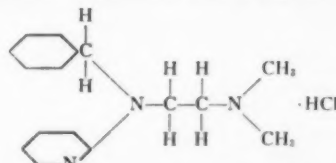
Dicoumarol

FIG. 2.

From the standpoint of the clinician, an extremely important aspect of this concept is its influence upon chemotherapeutic research. In retrospect, the mode of action of several important drug groups can probably be explained by this phenomenon. As illustrations, one can cite the vitamin K-dicoumarol relationship as well as the recent spectacular applications of the anti-histaminic drugs. In the case of the former, the basic similarity of the chemical constitution of these two agents was pointed out by Witts¹³ (figure 2), and the suggestion made that dicoumarol exerts its effect by



Histamine



Pyribenzamine Hydrochloride

FIG. 3.

interfering with the utilization of vitamin K by the liver. Like histamine, most of the effective anti-histaminic drugs are derivatives of ethylamine (figure 3) and are believed to be effective because of competition with the

¹² WOOLEY, D. W.: Biological antagonisms between structurally related compounds, *Advances in Enzymology*, 1946, vi, 129.

¹³ WITTS, L. J.: Disturbances in coagulation of blood, *Glasgow Med. Jr.*, 1942, cxxxvii, 57.

former for attachment to specific cell receptors.¹⁴ Recent trials of a group of folic acid antagonists, notably aminopterin, in the therapy of acute leukemia represent a further extension of this chemotherapeutic principle.^{15, 16}

As a result of recent developments, based upon this concept, the narrow view of chemotherapy as the treatment of infectious diseases with chemical agents would no longer seem to be tenable. Chemotherapeutic agents which may produce bacteriostasis by interference with bacterial nutrition have been found to have a profound effect upon cellular metabolism in the animal body. In many instances there is striking similarity between the metabolic processes of bacteria and higher animals. The close interrelation of bacterial and animal nutrition is well exemplified in the rapid translation of the recently acquired knowledge of the nutritional requirement of *Lactobacillus casei* for folic acid and *Lactobacillus lactis* Dorner for vitamin B₁₂, to the therapy of human disease. Although most studies in this field during recent years have been concerned with the antagonism of essential metabolites by a variety of their structural analogues, the principle has already been extended to include materials other than essential metabolites. The problems which beset the experimentalist in this field are numerous and varied. Synthesis of analogues obviously requires prior knowledge of the structure of essential metabolites, many of which are still unknown. Many analogues, when synthesized, will have no clinical value because of toxicity. Although many brilliant chemotherapeutic successes of the past have been achieved empirically, there is reason to believe that the continued application of the principle of competitive antagonism of structurally related compounds will not only stimulate but expand the horizons of chemotherapy in its broadest sense.

MILTON S. SACKS

¹⁴ KRANTZ, J. C., JR., and CARR, C. J.: The pharmacologic principles of medical practice, 1949, Baltimore, p. 679.

¹⁵ FARRER, S., DIAMOND, L. K., MERCER, R. D., SYLVESTER, R. F., JR., and WOLFF, J. A.: Temporary remissions in acute leukemia in children produced by a folic acid antagonist, 4-amino pteroyl glutamic acid (aminopterin), New England J. Med., 1948, cccxxxviii, 787.

¹⁶ SACKS, M. S., and BRADFORD, G.: Unpublished observations.

REVIEWS

Diseases of the Fundus Oculi with Atlas. By ADALBERT FUCHS, M.D., e.o. Professor of Ophthalmology of the University of Vienna. Translated by ERICH PRESSBURGER, M.D.; Edited by ABRAHAM SCHLOSSMAN, M.D. First English edition, limited to 995 numbered copies. 337 pages (plus 44 pages illustrations in color); 19 x 27.5 cm. The Blakiston Co., Philadelphia. 1949. Price, \$30.00.

This handsomely bound volume, printed in limited edition, is based on the lecture courses on fundus disease which have been delivered by the author over the past 25 years, and was first published in German in 1943. The present edition contains a few additions to both the text and the illustrations of the previous issues. The book is an attempt to combine in one volume both a textbook and atlas of ophthalmoscopy.

As an atlas this book bears sad testimony to the decline of the printing art during the past generation. The height of the art as exemplified in ophthalmoscopic atlases was reached in the production of Oeller issued in successive fascicules over the years 1895 to 1924. These meticulous drawings, reproduced in marvelous perfection by the European printers, were for two generations the standard wall decorations of the lecture rooms of departments of ophthalmology in various European universities. Their accuracy is such that it is still possible, after all these years and in the light of more modern knowledge, to make new and more refined diagnoses on the cases presented.

The best modern atlas of ophthalmoscopy from the reproductive point of view is, unquestionably that of Wilmer, printed by Hoen in 1934. In accuracy of drawing and of reproduction, Wilmer's atlas is fully equal to that of Oeller, falling short only in the number of conditions portrayed. The illustrations of the Fuchs book are evidently based on drawings of very fine quality, but their reproduction in small scale and in somewhat garish colors leaves much to be desired.

The text also falls short of the desiderata in respect to a modern textbook of ophthalmoscopy. It is less complete and less imbued with modern medical teaching than, for instance, the "Diseases of the Retina" recently published by Elwyn. In fact, the medical literature of the last 20 years is hardly mentioned. Nevertheless, the combination of atlas and textbook has a merit of its own, and the amplification of the fundus drawings by illustrations, also, of the histological pictures in typical cases adds much to the value of the book.

Those ophthalmologists who were suckled in their professional training on the classical textbook of Ernst Fuchs, father of the present author, will find additional nostalgic value in the frequent references to the subsequent histories in some of the illustrative cases originally cited by the elder Fuchs.

JONAS FRIEDENWALD

Internal Medicine in General Practice. 2nd Ed. By ROBERT PRATT McCOMBS, B.S., M.D., F.A.C.P., Director of Postgraduate Teaching, Tufts College Medical School. 741 pages, 16.5 x 24.5 cm. W. B. Saunders Company, Philadelphia. 1947. Price, \$3.00.

This second edition continues like the first edition in the Osler tradition and integrates the major facets of Internal Medicine through the eyes of one man. In places it may seem somewhat oversimplified. But it is factual, concise, and the chapters are readable without being exhausting. Sections on psychiatry and peripheral vascular disease have been added. There are eight more pictures and 52 more pages. Otherwise it remains essentially the same in format and spirit. The initial

chapter on "Fundamentals of Diagnosis" still makes a good introduction to clinical medicine for students.

Some charts (cf. table 3) seem unduly elaborate and space wasting. One wonders why, in so compact a presentation, a large illustration of the Westergren apparatus is thought necessary, and why if one *technic* is detailed, the Wintrobe and others are not mentioned. The aerosol illustration similarly seems out of place here, though doubtless cuts of smaller models were not available then.

Chemotherapy is conservatively dealt with, though therapeutic testing is rather frequently suggested. Chemotherapy in "the mildly ill" is warned against and abandonment in any case if ineffective after 72 hours is properly emphasized.

Newer antitussics are available, so the occasional recommendation of "morphine or codein" for cough, without suggestion of less habit forming drugs may be disliked by some readers.

Some acknowledgment should be made of disease variability with climate and geography. For instance, virus pneumonia is "highly contagious" with "complications unusual." This is in line with Longcope's early report concerned with cases in the Middle Atlantic Region. In other areas, notably Hawaii, where the condition was probably first reported, it is not considered particularly contagious. A variety of complications has been reported, pleurisy, sterile abscesses, and bronchiectasis.

These exceptions are all relatively minor. The many good points far outweigh the few bad ones. The text continues to be a welcome, fresh approach in a field replete with older, overgrown, cumbersome books. It is a good review and point of occasional reference for general practitioner and specialist as well. It can be recommended to the intelligent layman for exposition of a modern point of view on internal medicine.

C. B. A.

Experimental Immunochemistry. By ELVIN A. KABAT, Ph.D., and MANFRED M. MAYER, Ph.D., with a Foreword by MICHAEL HEIDELBERGER, Ph.D. 575 pages; 24 x 15.5 cm. 1948. Charles C. Thomas, Publisher, Springfield, Illinois. Price, \$8.75.

One of the greatest deterrents to the increase of knowledge in medical sciences today is the progressive specialization of the individual disciplines. Any book which makes even a partial try at bridging the gap between two branches is likely to be worthwhile. This book is successful in presenting to the chemist the ideas and practices of the immunologist, and in presenting immunological facts to the chemist. It is written by two competent students of Heidelberg, the outstanding leader in this country in the field of immunochemistry.

The book has some theoretical discussion throughout, but it is mainly one for use in the laboratory. Part I: Immunological and Immunochemical Methodology; Part II: Applications and Uses of Quantitative Immunochemical Methods; Part III: Chemical and Physical Methods; and Part IV: Preparations, are the titles of the four main parts and are sufficient reason for Heidelberg's statement in the Preview that "the book is, therefore, more likely to gather acid spots and indicator stains on the laboratory table than to accumulate dust on the reference shelves."

It is too bad, then, that the laboratory worker will have to squint his eyes hard and long to read some of the very fine print in the tables throughout.

This is a book of great value to all experimental workers in infectious diseases, allergy and biochemistry.

F. B. B.

Advances in Pediatrics. Volume 3. Editorial Board: S. Z. LEVINE, ALLAN M. BUTLER, L. EMMETT HOLT, JR., and A. ASHLEY WEECH. 363 pages; 16 x 24 cm. Interscience Publishers, Inc., New York 3, N. Y. 1948. Price, \$7.50.

This is the third volume of a personalized monographic presentation of pediatric subjects of current interest. The topics are written by authorities in their respective fields. The present issue contains eight monographs. Those by Dr. Milton Senn, "Emotions and Symptoms in Pediatric Practice," and Dr. Hilde Bruch, "Puberty and Adolescence: Psychologic Considerations," are representative of current pediatric thinking. The articles are well organized and offer physicians an opportunity to keep abreast of pediatric progress.

J. E. B.

Gardiner's Handbook of Skin Diseases. Revised by JOHN KINNEAR, O.B.E., T.D., M.D., M.R.C.P. (Ed.). 250 pages; 13 x 19.5 cm. The Williams and Wilkins Company, Baltimore. 1948. Price, \$4.50.

The author has presented a small, well written text which he has illustrated with a number of excellent black and white photographs and color plates. As stated in the preface this is a handbook and is not intended to replace a larger text. It deals adequately with the commoner skin diseases and briefly mentions some of the rarer ones. There are some minor variations between the terminology used in this book and those in common usage in the United States and some of the therapeutic suggestions are seldom followed in this country. Unfortunately, the author has not stressed the importance of the dark field examination as the most important diagnostic procedure in early syphilis, but rather stresses the convenience of the serologic test for syphilis. The chapters on fungus diseases are adequate. There is an interesting and practical chapter on the toxic dermatoses, under which heading the author also discusses eczema. The text is recommended for use by the general practitioner, and also by the student. It contains much valuable information in condensed form.

H. M. R.

Dr. W. C. Röntgen. By OTTO GLASSER, Cleveland Clinic Foundation. 169 pages; 14.5 x 22 cm. Charles C. Thomas, Springfield. 1945. Price, \$4.50.

Commemorating the fiftieth anniversary of the first report describing x-rays, Dr. Otto Glasser has composed a small volume retelling the story of their discovery. The identification of x-rays by W. C. Röntgen has often been described in a sensational fashion. Much to the credit of the author, the events prior to their discovery are related in a simple style.

Little known scientific studies of Professor Röntgen are discussed and serve to broaden our admiration for this pure scientist. He apparently was well known among the German universities for his investigations in the properties of gases. It was not until after 1890 that he became interested in a new tool, the cathode ray tube. This small biography describes in detail the original work leading up to the demonstration of an unknown ray and the following studies of this ray. His first and subsequent reports are reprinted. These are of twofold interest: The physical principles as then known are described in these reports.

Many glimpses are afforded of the man, Röntgen. Doubtlessly, few of us today would have refused the easy offers that were made to secure nobility and a comfortable fortune, largely tax free. He had very human traits, since he served on several faculties, moving from one to the other depending on which university offered the best research facilities.

This biography should be required reading for roentgenologists. They would,

perhaps, complain less of their present equipment if they compared their "plight" to the technical problems faced by Professor Röntgen.

D. J. B.

BOOKS RECEIVED

Books received during February are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Aviation Medicine in Its Preventive Aspects: An Historical Survey. By JOHN F. FULTON, O.B.E., M.D., D.Sc., Sterling Professor of Physiology, Yale University. 174 pages; 22.5 × 14.5 cm. 1949. Oxford University Press, New York. Price, \$3.50.

Child Psychiatry. 2nd Ed. By LEO KANNER, M.D., Associate Professor of Psychiatry, The Johns Hopkins University, etc.; with Prefaces by JOHN C. WHITEHORN, M.D., Henry Phipps Professor of Psychiatry, The Johns Hopkins University; ADOLF MEYER, M.D., LL.D., Henry Phipps Professor Emeritus of Psychiatry, The Johns Hopkins University, and EDWARD A. PARK, M.D., Professor Emeritus of Pediatrics, The Johns Hopkins University. 752 pages; 26.5 × 16 cm. 1949. Charles C. Thomas, Publisher, Springfield, Illinois. Price, \$8.50.

Clinical Case-Taking: Guides for the Study of Patients; History-Taking and Physical Examination or Semiology of Disease in the Various Systems. 4th Ed. By GEORGE R. HERRMANN, M.D., Ph.D., Professor of Medicine, University of Texas. 240 pages; 22.5 × 14.5 cm. 1949. The C. V. Mosby Company, Saint Louis. Price, \$3.50.

Diabetes and Its Treatment. By JOSEPH H. BARACH, M.D., F.A.C.P., Associate Professor Medicine, University of Pittsburgh, etc. 326 pages; 24.5 × 16.5 cm. 1949. Oxford University Press, New York. Price, \$10.00.

Diabetic Menus, Meals and Recipes. By BETTY M. WEST; Introduction by RUSSELL F. RYPINS, M.D., Chief, Diabetic Clinic, Mt. Zion Hospital, San Francisco. 254 pages; 22 × 14.5 cm. 1949. Doubleday & Company, New York. Price, \$2.95.

Diseases of the Fundus Oculi with Atlas—First English Edition (Limited Edition of 995 numbered copies). By ADALBERT FUCHS, M.D., e.o. Professor of Ophthalmology, University of Vienna; Translated by ERICH PRESSBURGER, M.D.; Edited by ABRAHAM SCHLOSSMAN, M.D. 337 pages, plus 44 pp. illus. in color; 27.5 × 19 cm. 1949. The Blakiston Company, Philadelphia. Price, \$30.00.

Doctors of Infamy: The Story of the Nazi Medical Crimes. By ALEXANDER MITSCHERLICH, M.D., Head of the German Medical Commission to Military Tribunal No. 1, Nuremberg; Translated by HEINZ NORDEN; with Statements by Three American Authorities Identified with the Nuremberg Medical Trial: ANDREW C. IVY, M.D., Vice-President, University of Illinois, etc.; TELFORD TAYLOR, Brigadier General, U. S. Army, Chief of Counsel for War Crimes; and LEO ALEXANDER, M.D., Psychiatrist, Consultant to the Secretary of War and to the Chief of Counsel for War Crimes; and a Note on Medical Ethics by ALBERT DEUTSCH (Including the New Hippocratic Oath of the World Medical Association); 172 pages; 21.5 × 14.5 cm. 1949. Henry Schuman, Publisher, New York. Price, \$3.00.

*An Elementary Atlas of Cardiography: An Introduction to Electrocardiography and X-ray Examination of the Heart.** By H. WALLACE-JONES, M.D., M.Sc., F.R.C.P., Honorary Consulting Physician, Royal Liverpool United Hospital; E. NOBLE CHAMBERLAIN, M.D., M.Sc., F.R.C.P., Honorary Physician, Royal Liverpool United Hospital, and E. L. RUBIN, M.D., F.F.R., D.M.R.E., Honorary Radiologist, Royal Liverpool United Hospital. 108 pages; 23 × 14.5 cm. 1948. The Williams & Wilkins Company, Baltimore. Price, \$3.00.

Industrial Fluorosis: A Study of the Hazard to Man and Animals near Fort William, Scotland. Medical Research Council Memorandum No. 22. A Report to the Fluorosis Committee by JOHN N. AGATE, G. H. BELL, G. F. BODDIE, R. G. BOWLER, MONAMY BUCKELL, E. A. CHEESEMAN, T. H. J. DOUGLAS, H. A. DRUETT, JESSIE GARRAD, DONALD HUNTER, K. M. A. PERRY, J. D. RICHARDSON and J. B. DE V. WEIR. 131 pages; 24.5 × 15.5 cm. (paper-bound). 1949. His Majesty's Stationery Office, London. Price, 4 s. 0 d. net.

Maternity in Great Britain: A Survey of Social and Economic Aspects of Pregnancy and Childbirth undertaken by a Joint Committee of the Royal College of Obstetricians and Gynaecologists and the Population Investigation Committee. 252 pages; 22.5 × 14.5 cm. 1949. Oxford University Press, New York. Price, \$4.00.

Pathologie des Kohlehydratstoffwechsels. By PROF. DR. E. FRANK, Direktor der II. medizinischen Klinik der Universität Istanbul. 342 pages; 22.5 × 15.5 cm. 1949. Benno Schwabe & Co., Verlag, Basel; Imported by Grune & Stratton, Inc., New York. Price, fr. 24.

The Pharmacologic Principles of Medical Practice: A Textbook on Pharmacology and Therapeutics for Medical Students, Physicians, and the Members of the Professions Allied to Medicine. By JOHN C. KRANTZ, JR., Professor of Pharmacology, School of Medicine, University of Maryland, etc.; and C. JELLEFF CARR, Associate Professor of Pharmacology, School of Medicine, University of Maryland. 980 pages; 23.5 × 16 cm. 1949. The Williams & Wilkins Company, Baltimore. Price, \$10.00.

The Physiology of the Eye. By HUGH DAVSON, D.Sc. (Lond.), Honorary Research Associate, University College, London, etc.; with a Foreword by SIR STEWART DUKE-ELDER, K.C.V.O., M.A., D.Sc., Ph.D., M.D., F.R.C.S. 451 pages; 22.5 × 14 cm. 1949. The Blakiston Company, Philadelphia. Price, \$7.50.

Psychodynamics and the Allergic Patient. By HAROLD A. ABRAMSON, M.D., F.A.C.A., Associate Physician for Allergy, The Mount Sinai Hospital, New York, etc. Panel Discussion: RUDOLF L. BAER, M.D., ETHAN ALLAN BROWN, M.D., HAL M. DAVISON, M.D., R. O. SPURGEON ENGLISH, M.D., FRANK FREMONT-SMITH, M.D., J. A. P. MILLET, M.D., M. MURRAY PESHKIN, M.D., HOMER E. PRINCE, M.D., SANDOR RADO, M.D., and EDWARD WEISS, M.D. 81 pages; 20 × 13.5 cm. 1948. The Bruce Publishing Company, Saint Paul. An Official Publication of The American College of Allergists. Price, \$2.50.

The Venereal Diseases: A Manual for Practitioners and Students. 2nd Ed. By JAMES MARSHALL, M.D., B.S., M.R.C.S., L.R.C.P., Director, Venereal Diseases Clinic, Royal Northern Hospital, London, etc. 369 pages; 22 × 14 cm. 1949. Macmillan Company of London—Agents: Macmillan Company of New York. Price, \$5.50.

* Incorporating the Third Edition of "Electrocardiograms" with 100 illustrations.

COLLEGE NEWS NOTES

AMERICAN COLLEGE OF PHYSICIANS DIRECTORY TO BE PUBLISHED IN AUTUMN OF 1949

Prepublication orders had exceeded 2,000 by early March, assuring publication of the 1949 Directory of the American College of Physicians. Membership Rosters only have been published since the last Directory in 1941 because of the many changes and restrictions imposed by World War II and by excessive cost of printing since then. The Rosters served an important but limited need, and a full Directory containing current professional information about its members as well as up-to-date information concerning the organization and activities of the College, is greatly needed.

A Directory Information Form will be mailed this Spring to each member of the College including those newly elected during the 1949 Annual Session. The information which it contains when returned to the College will be used in preparing the member's Directory entries. Members are urged to read carefully the instructions printed on this form as to character and extent of information to be published in the Directory, and manner of presentation. They are also requested to return the forms as promptly as possible, for the preparation of a complete and accurate Directory is necessarily time-consuming and publication in the Autumn of 1949 is the goal.

The cost of the 1949 Directory if ordered in advance of publication is \$4.00 to members of the American College of Physicians, and \$5.00 to non-members, institutions, firms, etc., to be billed to all at time of delivery. The cost after publication date has not yet been set. Members who have not yet reserved their copies are urged to do so at once, using the Prepublication Directory Order Forms mailed to them in January and in February.

A. C. P. POSTGRADUATE COURSES

At this time, six of the Postgraduate Courses offered by the College on the Spring 1949 Schedule have been concluded.

There are still accommodations available in Course No. 7, Cardiovascular Disease, Philadelphia Institutions, May 2-7, 1949, Dr. William G. Leaman, Jr., Director; and in Course No. 9, Endocrinology, Tufts College Medical School, Boston, June 13-18, 1949, Dr. Edwin B. Astwood, Director. Course No. 8, Physiological Basis for Internal Medicine, University of Pennsylvania Graduate School of Medicine, Philadelphia, May 9-14, 1949, Dr. Julius H. Comroe, Jr., Director, is already greatly over-subscribed.

For the information of members of the College and readers of the *ANNALS OF INTERNAL MEDICINE*, the detailed outlines of Courses No. 7 and No. 9 follow. All registrations are handled through the Executive Secretary, American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa.

COURSE NO. 7—CARDIOVASCULAR DISEASE

(May 2-7, 1949)

Philadelphia Institutions

The American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa.

WILLIAM G. LEAMAN, JR., M.D., F.A.C.P., *Director*

(Minimal Registration, 50; Maximal Registration, 90)

Fees: A.C.P. Members, \$30.00. Non-members, \$60.00

Consulting Committee

Edward L. Bortz, M.D., F.A.C.P.
Charles L. Brown, M.D., F.A.C.P.
Thomas M. Durant, M.D., F.A.C.P.
William A. Jeffers, M.D.
Louis B. Laplace, M.D., F.A.C.P.
Thomas M. McMillan, M.D., F.A.C.P.
William D. Stroud, M.D., F.A.C.P.

Officers of Instruction

- Samuel Bellet, M.D., F.A.C.P., Assistant Professor of Cardiology, University of Pennsylvania Graduate School of Medicine; Clinical Assistant Professor of Medicine, Woman's Medical College of Pennsylvania; Associate Editor, American Heart Journal; Philadelphia, Pa.
- Charles L. Brown, M.D., F.A.C.P., Dean and Professor of Medicine. The Hahnemann Medical College and Hospital of Philadelphia, Philadelphia, Pa.
- Julius H. Comroe, Jr., M.D., F.A.C.P., Professor of Physiology and Pharmacology, University of Pennsylvania Graduate School of Medicine; Clinical Physiologist, Hospital of the University of Pennsylvania; Philadelphia, Pa.
- André F. Courmand, M.D., Associate Professor of Medicine, Columbia University College of Physicians and Surgeons, New York, N. Y.
- Arthur C. DeGraff, M.D., F.A.C.P., Samuel A. Brown Professor of Therapeutics and Chief of Cardiac Clinic, New York University College of Medicine; Visiting Physician, Bellevue Hospital, New York, N. Y.
- William Dock, M.D., F.A.C.P., Professor of Medicine, Long Island College of Medicine; Director of Medicine, Long Island Division, Kings County Hospital; Brooklyn, N. Y.
- Harry F. Dowling, M.D., F.A.C.P., Clinical Professor of Medicine, George Washington University School of Medicine; Chief, George Washington Medical Division, Gallinger Municipal Hospital; Washington, D. C.
- Robert D. Dripps, M.D., Associate Professor of Anesthesiology in Surgery, University of Pennsylvania School of Medicine and Graduate School of Medicine; Anesthesiologist, Hospital of the University of Pennsylvania, Philadelphia, Pa.
- Thomas M. Durant, M.D., F.A.C.P., Professor of Clinical Medicine, Temple University School of Medicine; Visiting Physician, Philadelphia General Hospital; Philadelphia, Pa.
- Joseph Edeiken, M.D., F.A.C.P., Instructor in Medicine, University of Pennsylvania School of Medicine; Cardiologist, Medical Service No. 1, Mount Sinai Hospital; Philadelphia, Pa.
- William E. Ehrich, M.D., Professor of Pathology and Chairman of the Department of Pathology, University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa.
- Mortimer S. Falk, M.D., Assistant Instructor in Dermatology and Syphilology, University of Pennsylvania School of Medicine, Philadelphia, Pa.
- William I. Gefter, M.D., Clinical Assistant Professor of Medicine, Woman's Medical College of Pennsylvania, Philadelphia, Pa.
- Emanuel Goldberger, M.D., Lecturer in Medicine, Columbia University College of Physicians and Surgeons; Adjunct Physician, Montefiore Hospital for Chronic Diseases; Cardiographer and Associate Physician, Lincoln Hospital; New York, N. Y.
- Burton E. Hamilton, M.D., F.A.C.P., Instructor in Medicine, Harvard Medical School (Courses for Graduates); Cardiologist, Boston Lying-In Hospital and New England Deaconess Hospital; Consultant in Cardiology, Palmer Memorial Hospital; Boston, Mass.

- John P. Hubbard, M.D., Assistant Professor of Pediatrics, University of Pennsylvania School of Medicine, Philadelphia, Pa.
- Harold L. Israel, M.D., F.A.C.P., Assistant Professor of Medicine, Woman's Medical College of Pennsylvania; Assistant Visiting Physician, Philadelphia General Hospital; Philadelphia, Pa.
- Julian Johnson, M.D., F.A.C.S., Associate Professor of Surgery, University of Pennsylvania School of Medicine, Philadelphia, Pa.
- Louis N. Katz, M.D., F.A.C.P., Director of Cardiovascular Research, Michael Reese Hospital; Professorial Lecturer in Physiology, University of Chicago; Chicago, Ill.
- Seymour S. Kety, M.D., Professor of Clinical Physiology, University of Pennsylvania Graduate School of Medicine; Associate Clinical Physiologist, Hospital of the University of Pennsylvania; Philadelphia, Pa.
- Louis B. LaPlace, M.D., F.A.C.P., Associate in Medicine, Jefferson Medical College of Philadelphia, Philadelphia, Pa.
- William G. Leaman, Jr., M.D., F.A.C.P., Professor of Medicine and Chairman of the Department of Medicine, Woman's Medical College of Pennsylvania; Visiting Physician, Philadelphia General Hospital; President, Philadelphia Heart Association; Philadelphia, Pa.
- Leo Loewe, M.D., Assistant Professor of Clinical Medicine, Long Island College of Medicine; Attending Physician and Director of Thrombo-embolic Research Unit, Jewish Hospital; Brooklyn, N. Y.
- Alexander Margolies, M.D., F.A.C.P., Assistant Professor of Clinical Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pa.
- H. M. Marvin, M.D., Associate Clinical Professor of Medicine, Yale University School of Medicine; Attending Physician, Grace-New Haven Community Hospital; President-Elect, American Heart Association; New Haven, Conn.
- Thomas M. McMillan, M.D., F.A.C.P., Professor of Clinical Medicine, School of Medicine, and Associate Professor of Cardiology, Graduate School of Medicine, University of Pennsylvania; Chief of Division of Cardiology, Philadelphia General Hospital; Editor-in-Chief, American Heart Journal; Philadelphia, Pa.
- Hugh Montgomery, M.D., F.A.C.P., Assistant Professor of Clinical Medicine, University of Pennsylvania School of Medicine; Physician-in-Charge, Peripheral Vascular Section, Hospital of the University of Pennsylvania; Philadelphia, Pa.
- Meyer Naide, M.D., Associate in Medicine, University of Pennsylvania School of Medicine; Physician-in-Charge, Peripheral Vascular Clinic, Mount Sinai Hospital; Philadelphia, Pa.
- Herman W. Ostrum, M.D., Assistant Professor Radiology, University of Pennsylvania Graduate School of Medicine; Roentgenologist, Philadelphia General Hospital, Philadelphia, Pa.
- George A. Perera, M.D., Assistant Professor of Medicine, Columbia University College of Physicians and Surgeons, New York, N. Y.
- I. S. Ravdin, M.D., F.A.C.S., John Rhea Barton Professor of Surgery and Director of the Harrison Department of Surgical Research, University of Pennsylvania School of Medicine; Professor of Surgery, University of Pennsylvania Graduate School of Medicine; Philadelphia, Pa.
- Hobart A. Reimann, M.D., F.A.C.P., McGee Professor of the Principles and Practice of Medicine, Jefferson Medical College of Philadelphia, Philadelphia, Pa.
- George P. Robb, M.D., F.A.C.P., Consultant in Cardiology, Cardiovascular Research Unit, Veterans Administration; Consultant in Cardiology to the Surgeon General, U. S. Army; Assistant Medical Director, Metropolitan Life Insurance Co., New York, N. Y.

- Howard A. Rusk, M.D., F.A.C.P., Professor and Chairman of the Department of Rehabilitation and Physical Medicine, New York University College of Medicine; Chief of Rehabilitation Service, Bellevue Hospital; Director, New York University-Bellevue Medical Center Institute of Rehabilitation and Physical Medicine; New York, N. Y.
- Lauren H. Smith, M.D., F.A.C.P., Professor of Psychiatry and Chairman of the Department of Psychiatry, University of Pennsylvania Graduate School of Medicine; Administrator and Physician-in-Chief, Institute of the Pennsylvania Hospital; Philadelphia, Pa.
- Reginald H. Smithwick, M.D., F.A.C.S., Professor of Surgery, Boston University School of Medicine, Surgeon-in-Chief, Massachusetts Memorial Hospitals; Boston, Mass.
- Isaac Starr, M.D., Milton Bixler Hartzell Research Professor of Therapeutics, University of Pennsylvania School of Medicine, Philadelphia, Pa.
- Eugene A. Stead, Jr., M.D., F.A.C.P., Professor of Medicine, Duke University School of Medicine; Physician-in-Chief, Duke Hospital; Durham, N. C.
- William D. Stroud, M.D., F.A.C.P., Professor of Cardiology, University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa.
- Helen B. Taussig, M.D., Associate Professor of Pediatrics, Johns Hopkins University School of Medicine; Director Children's Cardiac Clinic at the Harriet Lane Home of the Johns Hopkins Hospital; Baltimore, Md.
- Harry E. Ungerleider, M.D., F.A.C.P., Medical Director, Research, The Equitable Life Assurance Society of the United States, New York, N. Y.
- S. O. Waife, M.D., Instructor in Medicine, Woman's Medical College of Pennsylvania; Assistant Director in Charge of Medical Education, Philadelphia General Hospital; Philadelphia, Pa.
- Paul D. White, M.D., F.A.C.P., Clinical Professor of Medicine, Harvard Medical School; Physician, Massachusetts General Hospital; Consultant in Cardiovascular Disease, National Heart Institute, Bethesda; Boston, Mass.
- John H. Willard, M.D., F.A.C.P., Associate Professor of Medicine, Woman's Medical College of Pennsylvania; Assistant Professor of Gastro-enterology, University of Pennsylvania Graduate School of Medicine; Philadelphia, Pa.
- Charles C. Wolferth, M.D., F.A.C.P., Professor of Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pa.
- Francis C. Wood, M.D., F.A.C.P., Professor of Medicine and Chairman of the Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pa.
- Wallace M. Yater, M.D., F.A.C.P., Director of the Yater Clinic; Formerly Professor of Medicine, Georgetown University School of Medicine; Washington, D. C.

This course will place emphasis on recent advances, including current knowledge, diagnosis, and treatment. Some attention will be given to such subjects as electrocardiography, radiology, catheterization of the heart, and the surgical treatment of special cardiac conditions. The course will include lectures, panel discussions, and, on two afternoons, suitable clinical demonstrations.

The lectures will be given in the new Auditorium of the American College of Physicians' Building, 4200 Pine St., Philadelphia, and the clinical work, Wednesday afternoon and Friday afternoon, will be given in the Surgical Amphitheatre of the Philadelphia General Hospital, 34th St. and Curie Ave., Philadelphia, Pa.

Courtesy of the Library of the College of Physicians of Philadelphia will be extended to registrants of the course. A reception and buffet supper will be given for members of the class and their wives or relatives at the College Headquarters on the first evening, May 2. Other social events will be arranged, participation to be optional.

*Outline of Course**Monday, May 2.*

A.M. Session.

- 9:00- 9:15 Introductory Remarks and Announcements.
Dr. Leaman.
- 9:15-10:00 Psychiatric Treatment in Cardiovascular Conditions.
Dr. Smith.
- 10:00-10:45 Clinical Features of the Commoner Types of Congenital Cardiac Defects.
Dr. Taussig.
- 10:45-11:00 Intermission.
- 11:00-11:45 Cardiac Catheterization in the Diagnosis of Congenital Cardiac Defects.
Dr. Cournand.
- 11:45-12:30 Surgical Treatment of Congenital Cardiac Defects.
Dr. Johnson.

P.M. Session.

- 2:00- 2:50 Clinical Features of the Commoner Types of Congenital Cardiac Defects (concluded).
Dr. Taussig.
- 2:50- 3:45 Angiocardiography.
Dr. Robb.
- 3:45- 4:00 Intermission.
- 4:00- 5:00 Cardiac Enlargement.
Dr. Ungerleider.
- 5:30 RECEPTION AND BUFFET SUPPER for Members of the Course and their Wives at the College Headquarters, 4200 Pine Street.

Tuesday, May 3.

A.M. Session.

- 9:00- 9:50 Pathogenesis of Rheumatic Fever.
Dr. Ehrich.
- 9:50-10:45 Clinical Aspects of Rheumatic Heart Disease.
Dr. LaPlace.
- 10:45-11:00 Intermission.
- 11:00-11:45 Comments on the Treatment of Rheumatic Fever.
Dr. Hubbard.
- 11:45-12:30 Question and Answer Period. Rheumatic Fever and Rheumatic Heart Disease.
Drs. Ehrich, LaPlace, Hubbard, Margolies and Leaman.

P.M. Session.

- 2:00- 2:50 Some Observations on Penicillin Treatment in Cardiovascular Syphilis.
Drs. Edeiken and Falk.
- 2:50- 3:45 Subacute Bacterial Endocarditis: Diagnosis and Present Day Treatment.
Dr. Loewe.
- 3:45- 4:00 Intermission.
- 4:00- 5:30 Acute Myocarditis. A Panel Discussion.
Drs. Loewe, Geffer, Dowling, Reimann and Leaman.

Wednesday, May 4.

A.M. Session.

- 9:00- 9:50 The Treatment of the Cardiac Arrhythmias.
Dr. Bellet.
9:50-10:30 Anti-Coagulant Therapy.
Dr. Yater.
10:30-10:45 Pulmonary Arteriovenous Fistula.
Dr. Yater.
10:45-11:00 Intermission.
11:00-11:50 Recent Advances in the Treatment of Peripheral Vascular Disorders.
Dr. Naide.
11:50-12:30 Thrombosis and Embolism. A Panel Discussion.
Drs. Yater, Montgomery, Naide, Ravdin and Leaman.

P.M. Session.

Surgical Amphitheatre, Philadelphia General Hospital
34th Street and Curie Avenue

- 2:00-2:30 Management of Acute Myocardial Infarction in the Diabetic Patient.
Dr. Waife.
2:30- 3:00 The Physiology and Pharmacology of the Coronary Circulation.
Dr. Kety.
3:00- 3:15 Intermission.
3:15- 4:45 Recent Advances in Electrocardiography.
Dr. Katz.
4:45- 5:30 Some Facts Concerning Cholesterol Metabolism and Their Clinical
Application.
Dr. Katz.
5:30- 6:00 Government Aids in Cardiovascular Research.
Dr. White.

Thursday, May 5.

A.M. Session.

- 9:00-10:15 Pericarditis. Diagnosis and Management.
Drs. McMillan, Bellet and Ostrum.
10:15-10:45 The Effect of Nicotine on the Cardiovascular System.
Dr. Comroe.
10:45-11:00 Intermission.
11:00-11:50 Unipolar Leads.
Dr. Goldberger.
11:50-12:30 Question and Answer Period. Electrocardiography.
Drs. Bellet, Goldberger, McMillan, Wood and Wolferth.

P.M. Session.

- 2:00- 2:50 Diet and Rest in Congestive Cardiac Failure.
Dr. Dock.
2:50- 3:50 Modern Aspects of Digitalis Therapy.
Dr. DeGraff.
3:50- 4:00 Intermission.
4:00- 4:40 Oxygen Therapy.
Dr. Comroe.
4:40- 5:30 Mercurial Diuretics.
Dr. Durant.

Evening Session

- 8:30 This meeting will be held at the College of Physicians of Philadelphia, 19 S. 22nd Street (Mitchell Hall, 2nd floor). It will be a joint meeting with the Philadelphia Heart Association and Section on General Medicine, College of Physicians of Philadelphia.

THE MECHANISM OF CONGESTIVE HEART FAILURE

EUGENE A. STEAD, JR., M.D., F.A.C.P.

Discussers: Drs. Starr and Stroud.

Friday, May 6.

A.M. Session.

- 9:00- 9:50 The Evaluation of the Cardiac Patient as a Surgical Risk.
Dr. Wood.
- 9:50-10:45 The Heart in Pregnancy.
Dr. Hamilton.
- 10:45-11:00 Intermission.
- 11:00-12:00 The Problem of Anesthesia in the Presence of Heart Disease.
Dr. Dripps.
- 12:00-12:30 The Heart in Surgery. A Panel Discussion.
Drs. Dripps, Wood, Johnson, Hamilton and Leaman.

P.M. Session.

Surgical Amphitheatre, Philadelphia General Hospital
34th Street and Curie Avenue

- 2:00- 3:00 The Medical Treatment of Coronary Heart Disease.
Dr. Marvin.
- 3:00- 3:45 The Medical Treatment of Hypertensive Cardiovascular Disease.
Dr. Perera.
- 3:45- 4:00 Intermission.
- 4:00- 5:00 The Surgical Treatment of Hypertension.
Dr. Smithwick.
- 5:00- 5:45 Question and Answer Period.
Drs. Marvin, Perera, Brown, Smithwick, Stroud and Leaman.

Saturday, May 7.

A.M. Session.

- 9:00- 9:30 Pulmonary Heart Disease.
Dr. Israel.
- 9:30-10:00 Cardiac Symptoms Secondary to Gastrointestinal Tract Disturbances.
Dr. Willard.
- 10:00-11:00 Some Problems in the Rehabilitation of the Cardiac Patient.
Dr. Rusk.
- 11:00-11:15 Intermission.
- 11:15-12:30 Review of Clinical Electrocardiography (Case Studies from the Heart Station, Philadelphia General Hospital).
Drs. Bellet and McMillan.

COURSE No. 9—ENDOCRINOLOGY

(June 13-18, 1949)

Tufts College Medical School (Postgraduate Division), Boston, Mass.

Director

EDWIN B. ASTWOOD, M.D., F.A.C.P.

Associate Directors

E. W. DEMPSEY, Ph.D.

ROY O. GREEP, Ph.D.

(Minimal Registration, 40; Maximal Registration, 100)

Fees: A.C.P. Members, \$30.00. Non-members, \$60.00

Officers of Instruction

- Fuller Albright, M.D., Associate Professor of Medicine, Harvard Medical School; Physician, Massachusetts General Hospital.
- E. B. Astwood, M.D., Ph.D., F.A.C.P., Research Professor of Medicine, Tufts College Medical School; Endocrinologist, Joseph H. Pratt Diagnostic Hospital.
- Joseph C. Aub, M.D., Professor of Research Medicine and Director of the Medical Laboratories of the Collis P. Huntington Memorial Hospital, Harvard Medical School; Physician, Massachusetts General Hospital.
- F. C. Bartter, M.D., Research Fellow in Medicine, Harvard Medical School; Clinical and Research Fellow in Medicine, Massachusetts General Hospital.
- J. S. L. Browne, M.D., C.M., Ph.D., F.R.S.C., F.A.C.P., Professor of Medicine, McGill University Faculty of Medicine; Director, University Clinic, Royal Victoria Hospital; Montreal, Que., Can.
- Earle M. Chapman, M.D., F.A.C.P., Instructor in Medicine, Harvard Medical School; Associate Physician, Massachusetts General Hospital.
- George W. Crile, Jr., M.D., F.A.C.S., Member, Surgical Staff, Cleveland Clinic Foundation, Cleveland, Ohio.
- M. Edward Davis, M.D., F.A.C.S., Joseph Bolivar DeLee Professor of Obstetrics and Gynecology, University of Chicago; Obstetrician and Gynecologist, Chicago Lying-In Hospital, Chicago, Ill.
- Edward W. Dempsey, Ph.D., Associate Professor of Anatomy, Harvard Medical School.
- Konrad Dobriner, M.D., Member, Sloan-Kettering Institute for Cancer Research, New York, N. Y.
- Kendall Emerson, Jr., M.D., Associate in Medicine, Harvard Medical School; Senior Associate in Medicine, Peter Bent Brigham Hospital.
- Earl T. Engle, Ph.D., Professor of Anatomy, Columbia University College of Physicians and Surgeons, New York, N. Y.
- John W. Everett, Ph.D., Associate Professor of Anatomy, Duke University School of Medicine, Durham, N. C.
- Louis F. Fieser, Ph.D., Sheldon Emery Professor of Organic Chemistry, Harvard University, Cambridge, Mass.
- Robert Gaunt, Ph.D., Professor of Zoology, Syracuse University, Syracuse, N. Y.
- Roy O. Grep, Ph.D., Associate Professor of Dental Science, Harvard School of Dental Medicine.
- Carl G. Hartman, Ph.D., Director, Division of Physiology, Ortho Research Foundation, Raritan, N. J.

- Roy Hertz, M.D., Ph.D., Assistant Clinical Professor of Medicine, The George Washington University School of Medicine; Chairman, Endocrinology Section, National Cancer Institute; Washington, D. C.
- Frederick L. Hisaw, Ph.D., Professor of Zoology, Harvard University, Cambridge, Mass.
- Roy G. Hoskins, M.D., Ph.D., Consultant in Medical Sciences, Boston Branch Office of Naval Research.
- John Eager Howard, M.D., Associate Professor of Medicine, Johns Hopkins University School of Medicine, Baltimore, Md.
- Dwight J. Ingle, Ph.D., Senior Research Scientist (Physiology), Research Laboratories, The Upjohn Company, Kalamazoo, Mich.
- F. D. W. Lukens, M.D., Associate Professor of Medicine and Director of the George S. Cox Medical Research Institute, University of Pennsylvania School of Medicine, Philadelphia, Pa.
- E. Perry McCullagh, M.D., F.A.C.P., Director, Section on Endocrinology and Metabolism, Cleveland Clinic Foundation, Cleveland, Ohio.
- Gregory Pincus, Sc.D., Director of Laboratories, Worcester Foundation for Experimental Biology; Research Professor of Physiology, Tufts College Medical School; Shrewsbury, Mass.
- John Rock, M.D., Clinical Professor of Gynecology, Harvard Medical School; Visiting Surgeon, Free Hospital for Women; Consulting Obstetrician, Massachusetts General Hospital.
- Jane A. Russell, Ph.D., Instructor in Physiological Chemistry, Yale University School of Medicine, New Haven, Conn.
- George Sayers, Ph.D., Associate Professor of Pharmacology, University of Utah College of Medicine, Salt Lake City, Utah.
- Hans Selye, M.D., Ph.D., D.Sc., Professor of Experimental Medicine and Surgery, and Director of the Institute of Experimental Medicine and Surgery, University of Montreal Faculty of Medicine, Montreal, Que., Can.
- Malcolm M. Stanley, M.D., Instructor in Medicine, Tufts College Medical School; Research Associate in Medicine, Joseph H. Pratt Diagnostic Hospital.
- Somers H. Sturgis, M.D., Clinical Associate in Gynecology, Harvard Medical School; Assistant Surgeon, Massachusetts General Hospital; Chief, Vincent Memorial Hospital Research Laboratory.
- S. J. Thannhauser, M.D., Ph.D., Professor of Clinical Medicine, Tufts College Medical School; Associate Physician-in-Chief, Joseph H. Pratt Diagnostic Hospital.
- W. P. VanderLaan, M.D., Assistant Professor of Medicine, Tufts College Medical School; Assistant Physician, Joseph H. Pratt Diagnostic Hospital.
- H. B. Van Dyke, M.D., Ph.D., Hosack Professor of Pharmacology, Columbia University College of Physicians and Surgeons, New York, N. Y.
- A. E. Wilhelmi, Ph.D., Assistant Professor of Physiological Chemistry, Yale University School of Medicine, New Haven, Conn.

This course is designed for internists who are especially interested in endocrinology and who desire further training in the basic physiology and biochemistry of the subject.

A Presiding Chairman has been assigned to each session to guide the discussion, and various faculty members will be present to provide an opportunity for free discussion among the faculty and the students.

The course will be held in the *New England Medical Center* (Joseph H. Pratt Diagnostic Hospital, Ziskind Research Laboratories, Boston Floating Hospital, Boston Dispensary, and the New England Center Hospital).

*Outline of Course**Monday, June 13.*

A.M. Session. DR. ROY G. HOSKINS, Chairman.

9:00- 9:15 Registration.

9:15- 9:30 Introduction.

Dr. Hoskins.

9:30-10:15 Histochemistry of the Endocrine Glands.

Dr. Dempsey.

10:30-11:15 Integrative Functions of the Endocrine System.

Dr. Greep.

11:30-12:15 Experimental and Clinical Aspects of Nutrition and Endocrine Function.

Dr. Hertz.

P.M. Session. DR. S. J. THANNHAUSER, Chairman.

2:00- 2:45 Parathyroids and Mineral Metabolism.

Dr. Greep.

3:00- 3:45 Tetany and Hyperparathyroidism.

Dr. Bartter.

4:00- 5:00 Metabolic Bone Disease and Hyperadrenocorticism.

Dr. Albright.

Tuesday, June 14.

A.M. Session. DR. GREGORY PINCUS, Chairman.

9:00- 9:45 Hormonal and Neural Factors Regulating the Chronology of the Mam-malian Reproductive Cycle.

Dr. Everett.

10:00-10:45 Endocrine Control of Menstrual Cycle.

Dr. Hisaw.

11:00-12:00 The Physiological Significance of the Common Menstrual Irregu-larities.

Dr. Davis.

P.M. Session. DR. JOHN ROCK, Chairman.

2:15- 2:45 Clinical Investigation of Sterility in Women.

Dr. Sturgis.

3:00- 4:00 The Testis Biopsy in Infertility.

Dr. Engle.

4:15- 5:15 Hypogonadism and Sterility in the Male.

Dr. McCullagh.

Wednesday, June 15.

A.M. Session. DR. EARL T. ENGLE, Chairman.

9:00- 9:45 Migration and Maturation of Sperm in the Male Genital Tract.

Dr. Hartman.

10:00-10:45 Transport and Survival of Sperm in the Female Genital Tract.

Dr. Hartman.

11:00-12:00 The Physiological Significance of the Posterior Pituitary Gland.

Dr. Van Dyke.

P.M. Session. DR. H. B. VAN DYKE, Chairman.

2:00- 2:45 Adrenal Cortex in Salt-and-Water Metabolism.

Dr. Gaunt.

- 3:00- 3:45 Regulation of the Secretory Activity of the Adrenal Cortex.
Dr. Sayers.
4:00- 4:45 The Relationship of the Adrenal Cortex to Organic Metabolism.
Dr. Ingle.

Thursday, June 16.

- A.M. Session. DR. J. S. L. BROWNE, Chairman.
9:00- 9:45 Addison's Disease.
Dr. Emerson.
10:00-11:00 Preparation and Actions of Anterior Pituitary Growth Hormone.
Dr. Wilhelmi.
11:15-12:15 Metabolic Effects of the Anterior Pituitary.
Dr. Russell.
P.M. Session. DR. GREGORY PINCUS, Chairman.
2:00- 2:45 Factors Regulating Adrenal Cortical Activity Under Normal and Pathological Conditions.
Dr. Selye.
3:00- 4:00 Chemistry of the Steroid Hormones.
Dr. Fieser.
4:15- 5:15 Steroid Hormone Metabolism.
Dr. Dobriner.

THURSDAY EVENING—Dinner

Friday, June 17.

- A.M. Session. DR. GEORGE W. CRILE, JR., Chairman.
9:00- 9:45 Physiology of the Thyroid Gland.
Dr. Astwood.
10:00-10:45 Diagnosis of Thyroid Disorders.
Dr. Howard.
11:00-11:30 Evaluation of Human Thyroid Function with I¹³¹.
Dr. Stanley.
11:45-12:15 Antithyroid Compounds in Hyperthyroidism.
Dr. VanderLaan.
P.M. Session. DR. JOHN EAGER HOWARD, Chairman.
2:00- 2:45 Use of Radioactive Iodine in the Therapy of Hyperthyroidism and Thyroid Tumors.
Dr. Chapman.
3:00- 4:00 Indications for Surgical Treatment of Thyroid Diseases.
Dr. Crile.
4:15- 5:00 General Discussion of Therapy in Thyroid Diseases.
Dr. Howard, Moderator.

Saturday, June 18.

- A.M. Session. DR. JOSEPH C. AUB, Chairman.
9:00-10:00 The Pathogenesis of Diabetes.
Dr. Lukens.
10:15-11:00 Structure and Endocrine Function of the Placenta.
Dr. Dempsey.
11:15-12:15 Endocrine Physiopathology of Pregnancy.
Dr. Browne.

A REPORT ON POSTGRADUATE COURSE No. 3, CLINICAL MEDICINE FROM THE
HEMATOLOGIC VIEWPOINT

The American College of Physicians had upon its Spring, 1949, schedule, February 14-19, a course entitled "Clinical Medicine from the Hematologic Viewpoint," organized and directed by Dr. Charles A. Doan, F.A.C.P., Dean and Professor of Medicine, Ohio State University College of Medicine, Columbus, Ohio. In addition to faculty members from the Ohio State University, Dr. Marion F. Beard, F.A.C.P., University of Louisville School of Medicine, Louisville; Dr. Theodore S. Evans, F.A.C.P., Yale University School of Medicine, New Haven; Dr. Malcolm Hargraves of the Mayo Clinic, Rochester; Dr. Henry E. Wilson, Jr., of Northwestern University Medical School, Chicago; Dr. Sloan J. Wilson of the University of Kansas School of Medicine, Kansas City; and Dr. Ernest von Lauda, Professor of Medicine at the University of Vienna, Vienna, Austria, constituted a Visiting Faculty.

One day each was devoted to the following general themes: the histo- and pathologic-physiology of the blood and blood-cell forming organs as the basis for a better understanding of human disease; the anemic states; the white blood cell dyscrasias; disease syndromes involving the spleen, liver and bone marrow; the hemorrhagic syndromes; miscellaneous topics. Forty-five physicians coming from various parts of the United States and Canada were registered in the course. Each afternoon they were divided into four groups for ward rounds, round table conferences and laboratory work with both supravital and fixed preparations. Those who were interested in the Regional American Red Cross Blood Center were taken for a personal inspection and tour of the Center one evening. A shipment of radio-active phosphorus from Oak Ridge was received during the week, and a group of interested persons from the class visited the laboratory where this was prepared for clinical therapeutic use. On another day, a special feature was the arrangement for a splenectomy with the fresh material carried directly to the laboratory for afternoon work; and a number of the men went to the operating room and observed the surgery. On one evening, the Department of Physics, with the Chairman of the Department as host, took thirty-five of the group to see the cyclotron and the demonstration of the physical apparatus with biological application such as the electron microscope, the Vandergraf generator and other apparatus significant in biological research. Even after the course was formally concluded at noon on Saturday, a number of the men remained in the afternoon for additional study of the fixed slides and the graphs and demonstrations which were prepared for them.

The course gave a considerable latitude in election for the men in a variety of experiences, and those who desired full-time with the microscopes were permitted to do so, while the clinicians who wanted more clinical outlets, were given the ward round opportunity.

Many niceties were introduced such as mid-morning and mid-afternoon recesses, the serving of coffee and tea and cookies, and an evening cocktail party and dinner the first day, at which Dr. Ernest von Lauda, Professor of Medicine at the University of Vienna, gave a talk on "The Present Status of Medicine in Europe." Members of the College who were registered in the course have expressed great appreciation of this excellent course.

ACP REGIONAL MEETING IN OMAHA

The Annual Regional Meeting of the College for the State of Nebraska was held at Omaha on February 19, 1949, under the direction of Dr. Joseph D. McCarthy, Governor for that state. Out of 66 members in the state, 52 were in attendance, 3

members came from Iowa, and there were 6 guests, making a total of 61. The attendance would have been greater except for hazardous road conditions resulting from sleet storms about the state.

A very excellent scientific program was rendered, under the Chairmanship of Dr. Adolph Sachs, F.A.C.P., a former Governor of that state. Dr. Walter L. Palmer, F.A.C.P., Chicago, Chairman of the Board of Governors of the American College of Physicians, was the chief guest speaker. He presented a paper entitled, "The Treatment of Intractable Peptic Ulcer," on the scientific program, and he addressed the dinner meeting in the evening on "Problems Confronting the American College of Physicians and the American Board of Internal Medicine."

The next Annual Regional Meeting for Nebraska will be held in Lincoln during February or March, 1950.

WESTERN MICHIGAN HELD ACP REGIONAL MEETING

Members of the American College of Physicians located in Western Michigan held a Regional Meeting at the Kent Country Club, Grand Rapids, Mich., February 23, 1949, under the Chairmanship of Dr. Gordon W. Balyeat, F.A.C.P.; 70 members of the College and guests were present.

The program consisted of the following: "The Use of Drugs in Vascular Disease," Noyes L. Avery, Jr., M.D., F.A.C.P.; "Laboratory Problems in the Serodiagnosis of Certain Mycotic Infections," Paul A. Van Pernis, M.D. (by invitation); "Albright's Syndrome," Gordon W. Balyeat, M.D., F.A.C.P.; "An Unusual Bone Disease," Carl B. Beeman, M.D., F.A.C.P. There were exhibits through the courtesy of C. Allen Payne, M.D., and others, and in the evening Dr. Burton R. Corbus, F.A.C.P., was toastmaster at a dinner at which Dr. Merrill Wells, F.A.C.P., gave an address of welcome, and Dr. Clarence W. Muehlberger, Chief Toxicologist at the Michigan State Department of Health Laboratories, gave an address, "Scientific Methods of Criminal Investigation."

UTAH-IDAHO REGIONAL MEETING

The 1949 meeting of members of the College in Utah and Idaho was held at the Salt Lake General Hospital, Salt Lake City, Utah, on March 4, 1949, through the collaboration of Louis E. Viko, M.D., F.A.C.P., Salt Lake City, Governor for Utah, Samuel M. Poindexter, M.D., F.A.C.P., Boise, Governor for Idaho, and Maxwell W. Wintrobe, M.D., F.A.C.P., Salt Lake City, Chairman of the Program Committee. First Vice President William S. Middleton, M.D., F.A.C.P., Madison, Wis., was the guest of honor; he conducted a clinical pathological conference and spoke at the dinner meeting on "Therapia Magna Sterilisans." A feature of the meeting was the round table discussion conducted at the luncheon by G. Gill Richards, M.D., F.A.C.P., Salt Lake City.

The following cases and papers were presented at the morning and afternoon sessions: J. C. Nunemaker, Spondylitis in Identical Twins Raised Apart; F. H. Tyler, Clinical Manifestations and Inheritance of Facioscapulohumeral Progressive Muscular Dystrophy; H. Brown, Potassium Metabolism in Diabetic Acidosis; H. H. Hecht, The Natural History of Coronary Artery Disease; R. D. Beech (Associate), An Unusual Case of Arterial Disease; Horace W. Davenport, Relationship of Electrolytes to Convulsive Seizures; Louis G. Moench, F.A.C.P., Some Somatic Aspects of Psychosomatic Medicine; G. R. Leymaster, Influenza Vaccines; B. V. Jager, Alterations of Serum Proteins in Disease; G. E. Cartwright, The Newer Knowledge of Pernicious Anemia;

J. F. Waldo, The Newer Antibiotics; P. F. Miner, Management of Bleeding Duodenal Ulcer; M. M. Wintrobe, F.A.C.P., Chemotherapy of Leukemia and Diseases Involving Lymph Nodes; Theodore C. Bauerlein, F.A.C.P., Gastroscopic Diagnosis of Stomach Lesions.

ADDITIONAL LIFE MEMBERS

The American College of Physicians takes pride in announcing that, by their recent subscriptions, the following Fellows have been added to the Roster of Life Members of the College:

J. Russel Brink, Grand Rapids, Mich.
Joseph E. J. Harris, Albuquerque, N. M.
George R. Lacy, Pittsburgh, Pa.
Harold W. Lovell, New York, N. Y.
Harold C. Lueth, Omaha, Nebr.
Carl L. Mauser, Oakland, Calif.
Lester Neuman, Washington, D. C.
John M. Rumsey, San Diego, Calif.
Ben Shenson, San Francisco, Calif.

MEETINGS OF OTHER SOCIETIES

The American Association of Railway Surgeons will hold its 61st Annual Meeting at the Drake Hotel, Chicago, Ill., on July 1 and 2, 1949.

The 15th Annual Meeting of the American College of Chest Physicians will be held at the Ambassador Hotel, Atlantic City, N. J., June 2 to 5, 1949.

The International Congress on Rheumatic Disease will be held at the Waldorf-Astoria Hotel, New York, N. Y., May 30 to June 3, 1949. More than 150 physicians from foreign countries are expected to attend. The meeting will contain morning plenary sessions and afternoon hospital clinics. The meeting is open; registration fee, \$10.00.

POSTGRADUATE COURSE IN SAN FRANCISCO

A postgraduate course of 12 weeks' length in Psychiatry and Neurology will be offered at the University of California Medical School (the Langley Porter Clinic), in San Francisco, August 29–November 18, 1949. The course will be full-time, and will be conducted by Karl M. Bowman, M.D., Professor of Psychiatry, Chairman. Tuition, \$200.00. For course outline, communicate with Stacy R. Mettier, M.D., Head of Postgraduate Instruction, Medical Extension, University of California Medical Center, San Francisco 22, Calif.

APPLICATIONS FOR RESEARCH FELLOWSHIPS IN SPINAL CORD DISEASE AND TRAUMA

Applications will be received to June 1, 1949, for a limited number of fellowships to facilitate investigation of spinal cord disease and trauma and the complications commonly associated with such disease and injury, by The National Paraplegia Foun-

dition. The Fellowships will be awarded by the Medical Advisory Committee, for the academic year 1949-50, and will carry a minimum stipend of \$3,000.00 a year. Candidates must demonstrate a capacity for medical research and must outline a program of meritorious study. Application forms may be secured from L. W. Freeman, M.D., Chairman, Medical Advisory Committee, National Paraplegia Foundation, Room 457, Hotel La Salle, Chicago 2, Ill.

THE UNIVERSITY OF VIENNA AGAIN OFFERS POSTGRADUATE COURSES

The University of Vienna has recently announced that its clinical facilities for postgraduate study of medicine and surgery are available to doctors from overseas, that accommodations are well organized and are being handled exclusively in Vienna by the Oesterreichische Verkehrsbureau, which coöperates with all travel agents. The Austrian State Tourist Department, 48 East 48th Street, New York 17, N. Y., is the North American representative.

Courses are available in General Pathology, Pathological Histology, Surgery, X-Ray Diagnosis, Clinical Differential Diagnosis, Hematology, Internal Diseases, Electrocardiography, Clinical Endoscopy, Obstetrics, Gynecology, Psychiatry, Neurology, Dermatology, Microscopy, Otology, Laryngology, and in many other fields.

Dr. J. Murray Kinsman, F.A.C.P., College Governor for the State of Kentucky, has been elected Dean of the University of Louisville School of Medicine, to assume office on July 1, 1949. Dr. John Walker Moore, present Dean, is resigning as of July 1, to return to private practice.

OBITUARIES

DR. LLEWELLYN R. COLE

Llewellyn Rathbun Cole, M.D., F.A.C.P., of Madison, Wis., died suddenly of a massive subarachnoid hemorrhage on December 31, 1948, at the age of 46.

Dr. Cole was born in Clintonville, Wis., December 17, 1902. He received his B.A. in 1926, and his doctorate in medicine in 1929, from the University of Wisconsin. After serving as resident physician in the Graduate Hospital, Philadelphia, from 1929 to 1931, he returned to the University of Wisconsin as an assistant physician in the Department of Student Health. In 1936, he became Assistant Professor of Clinical Medicine in the University of Wisconsin Medical School, and Director of Student Health. He was advanced to Professor of Clinical Medicine in 1938.

Dr. Cole retired in 1945 because of ill health, but returned to the University the following year as Co-ordinator of Graduate Medical Education, a position created to meet the increasing demands of the Medical School to extend medical education beyond the Campus. This opportunity enabled him to develop his previously recognized talents as a radio lecturer and a writer of script to bring the advances of science and health to radio listeners. In the following two and one half years of his life, he broadcast his radio program on the University station WHA. So successful was he that the officers of the State Medical Society invited him to take over their radio program, The March of Medicine, broadcast over 26 stations in the State.

Dr. Cole initiated a program to improve medical education and practice through a system of postgraduate medical short courses for general practitioners and refresher courses for specialists. He became a consultant on medical affairs to the President of the University and served on many University and Faculty committees. He was one of the planners of the "Wisconsin Center," a building to be used for the housing and instruction of groups coming to the University for short courses. To further medical education for the profession, Dr. Cole was organizing lectures to be broadcast over FM stations, as an experiment. In short, he took advantage of every means available for disseminating medical information to the profession and citizenry.

As a student Dr. Cole was elected to Alpha Omega Alpha. He held membership in the Dane County and State of Wisconsin Medical Societies, and was a Fellow of the American Medical Association. Elected a Fellow of the American College of Physicians in 1941, he gave valuable assistance to its regional and postgraduate programs. He was a senior staff member of the State of Wisconsin General Hospital.

With the death of Dr. Cole, we have lost a pioneer in health education, a gifted lecturer and writer, a counselor and coördinator of medical education, and an organizer and planner of medical courses.

KARVER L. PUESTOW, M.D., F.A.C.P.,

Governor for Wisconsin

DR. THOMAS BALFOUR DUNN

Dr. Thomas Balfour Dunn of Oakland, Calif., died suddenly at Fresno, on December 28, 1948. He was en route to Los Angeles to attend the Rose Bowl football game.

Dr. Dunn was born in Ventura, Calif., May 5, 1886. He received a B.S. degree in 1913, and his M.D. degree in 1916, both from the University of California. While still a senior medical student, he served an internship at the University of California Hospital. After graduation he received an honor internship in this hospital, serving from 1916 to 1917. During the years 1917 to 1920 he served in the U. S. Navy during World War I, being assigned to Asiatic duty. In 1920 Dr. Dunn entered medical practice at Shanghai, China, where he rapidly achieved prominence as an internist, enjoying a long and interesting career as chief of a diagnostic center. Many

important Chinese officials were patients of Dr. Dunn during his career in China, including Chiang Kai Shek and T. V. Soong. Dr. Dunn was a member of the Board of Governors of the County Hospital and the Shanghai General Hospital; served as President of the Shanghai Medical Society and the Foreign Practitioners' Medical Society. He was a Fellow of the London and Royal Societies of Tropical Medicine, and a member of the Chinese Medical Society.

During World War II he was imprisoned by the Japanese, losing all of his medical library, reprints and papers. In 1943 Dr. Dunn was returned to New York on the *Gripsholm* and was repatriated. He returned to California in 1944 and took up residence in Oakland, where he shortly became well established as a consultant in internal medicine. His appointments included the Staffs of the Samuel Merritt, Peralta, and Providence Hospitals, Oakland, and the Alta Bates Hospital in Berkeley. One of his first appointments after returning to California was as Lecturer in Tropical Medicine at the University of California Medical School, where considerable time was spent in establishing a clinic in Tropical Medicine and organizing the teaching of this subject.

Dr. Dunn was a diplomate of the Board of Internal Medicine and became a Fellow of the American College of Physicians in 1946. He was a member of the Alameda County and California State Medical Societies; a Fellow of the American Medical Association, the California Academy of Medicine and the American Society of Tropical Medicine.

Dr. Dunn possessed a distinguished bearing, a kindly, genial personality and a fund of common sense that attracted patients, and established contacts with his fellow practitioners. These factors led to a position of influence in his community during the too few years of life, after returning to his native California.

ERNEST H. FALCONER, M.D., F.A.C.P.

DR. LUIS ORTEGA

Dr. Luis Ortega of Havana, Cuba, died of cerebral hemorrhage on December 10, 1948, at the age of 76 years. He is survived by his wife, Mrs. Esperanza Ortega, a son, Dr. Luis Ortega, Jr., and six grandchildren.

Dr. Ortega graduated from the University of Havana in 1896. His high ranking led to his selection as intern, chief intern, and anesthesiologist in the "Nuestra Senora de las Mercedes" Hospital, now directed by his son, who is Assistant Professor of Clinical Medicine in the University of Havana. Following several years of full-time hospital work, Dr. Ortega received appointment, after competitive examination, as Associate Professor of Clinical Medicine in the University. He was later promoted to the head Professorship, to the Deanship of the School of Medicine, and to the Presidency of the University. At the time of his death, Dr. Ortega held the chair of Research Professor.

After World War I, Dr. Ortega pioneered in founding the "Ortega Clinic," with requirements for modern practice and group medicine similar to the best in the United States and Europe. His practice was very active with prominent patients and frequent consultations on difficult cases by his colleagues. All of his assistants are distinguished in their fields; some are Fellows of the American College of Physicians. He contributed greatly to the control of tuberculosis in Cuba, and served as president of the Cuban Society of Tuberculosis and of the National Board of Tuberculosis. His far reaching personality and outstanding capacity made him a great influence in Cuban medicine, and his accomplishments were recognized by his elections as president of the National College of Physicians, the Society of Clinical Studies, the Seventh National Medical Meeting, and the Section of Internal Medicine of the Eighth Pan American Meeting, among others.

Dr. Ortega was considered by local Fellows of the American College of Physicians to be the head of their group. He joined with others in Tampa in 1941, the year of his election to Fellowship, in establishing the College's growth in Havana.

Through his many medical papers, his teachings at the University, his success as a consultant, Dr. Ortega strongly influenced younger generations of physicians, impressing them with his knowledge of the best of European medicine and with his interest in the contributions of modern North American medicine. He was not only a very successful practitioner and man of science but a penetrating critic and a humanist with a clear philosophical mind. His passing has left a real sense of loss in the hearts of his patients, colleagues and pupils, but his spirit will certainly continue with them.

JOSÉ J. CENTURIÓN, M.D., F.A.C.P.,
Governor for Cuba

DR. CHARLES LEONARD OVERLANDER

Dr. Charles L. Overlander died December 16, 1948, at the age of 75. He was a self-effacing man of iron will, who had surmounted many difficulties and achieved success. He had contributed as a physician for 43 years to the health of the Boston community.

Dr. Overlander was Director of the Pathological Laboratory of the Brooks Hospital, Brookline, Mass., for 30 years. He graduated from the University of Ottawa, Ottawa, Kans., in 1896; later he endowed this University with a scholarship of \$10,000.00, for worthy students, particularly those who wished to enter scientific fields. He graduated from the University of Kansas School of Pharmacy in 1898. He received the Ph.B. degree in 1901 from the Sheffield Scientific School of Yale University, and then entered Harvard Medical School, from which he graduated cum laude in 1905. He subsequently interned at the Massachusetts General Hospital and the Children's Hospital. He was on the staff of the Boston Dispensary, 1908-1911, and was chemist to the Boston City Hospital from 1909 to 1917.

Dr. Overlander published articles in the Boston Medical and Surgical Journal, the Journal of the American Medical Association, the Interstate Medical Journal and the Lancet Clinic. He became a Fellow of the American College of Physicians in 1920, and was a member of the American Association for the Advancement of Science, the American Medical Association, American Society of Bacteriologists, Boston Bacteriological Club, Sigma Xi, Phi Rho Sigma, and the Harvard and Yale Clubs of Boston.

MAJOR GENERAL GEORGE C. BEACH, JR. (MC), U. S. ARMY

George Corwin Beach, Jr., Assistant Surgeon General and Commanding Officer of the Army Medical Center, Washington, D. C., died November 18, 1948, at the Walter Reed General Hospital.

Dr. Beach was born in Topeka, Kans., October 28, 1888. He attended Washburn College and graduated in 1911 from the University Medical College of Kansas City. He interned in the University Hospital, Kansas City, Mo., and in 1912 became a lieutenant in the Medical Reserve Corps of the U. S. Army. In 1916 he was commissioned in the Medical Corps. His subsequent assignments included tours of duty at Fort Monroe, Va., Camp Greene, Charlotte, N. C., Letterman General Hospital, San Francisco, Calif., General Dispensary, Washington, D. C., Sternberg General Hospital, Manila, Fort Sherman, C. Z., and Europe. From 1935 to 1939, Dr. Beach was Chief of Medical Service of the Station Hospital at Fort Leavenworth, Kans. During the years 1939-46, he was Chief of Medical Service and Commanding Officer of the Station Hospital at Fort Sam Houston, Tex.

Major General Beach became a fellow of the American College of Physicians in 1935. He was a fellow of the American Medical Association and a member of the Association of Military Surgeons of the United States. He was a diplomate of the American Board of Internal Medicine.

REAR ADMIRAL ROBERT G. DAVIS (MC), U. S. NAVY, RETIRED

Rear Admiral Davis died on November 8, 1948, in San Diego, Calif. He was born in Indianola, Iowa, on May 29, 1883, and received his education at Simpson College (B.S., 1905) and Rush Medical School (M.D., 1909).

Dr. Davis entered the U. S. Navy in 1912 and advanced through various ranks to Captain in 1937. During his service, Admiral Davis served at the Naval Hospitals at Great Lakes, Ill., Las Animas, Colo., Puget Sound, Wash., and San Diego, Calif., as well as on board the *Wright*, *Langley*, *Aroostook* and *Saratoga*. He did pioneer work in establishing aviation medicine in the Navy, studying problems and methods abroad and engaging in research and instruction in this field.

During World War II, Dr. Davis served as District Medical Officer of the 16th Naval District and as Medical Officer in Command of the Naval Hospital and Medical Supply Depot at Canacao, Philippine Islands, where he was captured by the enemy Japanese forces January 2, 1942, along with members of his hospital staff. He was liberated from a Japanese prison camp on August 30, 1945, in Mukden, Manchuria, after having been interned for 43 months. Upon returning to this country in September, 1945, he was assigned to duty as a member of the Naval Retiring Board, San Diego, Calif., and was placed on the retired list on October 1, 1946. Among the many decorations that he held was the Legion of Merit for service in combat.

Admiral Davis became a fellow of the American College of Physicians in 1932. He was also a member of the American Medical Association, the Association of Military Surgeons of the United States, and of the San Diego Academy of Medicine.

DR. MARK STEVENS KNAPP

Dr. Mark Stevens Knapp of Fenton, Mich., died on November 11, 1948, at the age of 76. Dr. Knapp received his B.S. in 1895 and his M.D. in 1898 from the University of Michigan. Following graduation, he practiced for many years in Flint, where he was Chief of Medicine at the Hurley Hospital for some time. He was also a member of the Advisory Staff of this Hospital and the Women's Hospital. In 1920, he became a fellow of the American College of Physicians, being one of the earliest members in Flint. In 1934, he became a director of the Horace H. Rackham and Mary A. Rackham Fund, and was active in this work for two years, when Ménière's disease compelled him to retire. Since then he had lived in retirement in Fenton.

DOUGLAS DONALD, M.D., F.A.C.P.,
Governor for Michigan

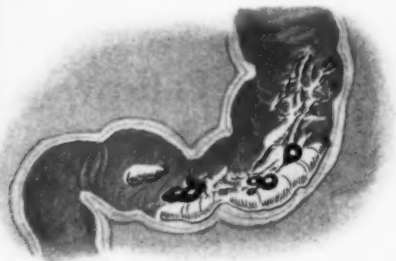
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